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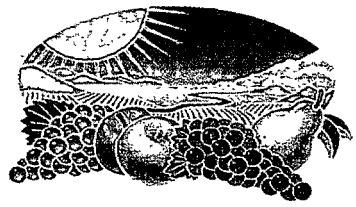
Original Submission



Providing World-Class, Natural Products To Improve People's Lives

January 28, 2003

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food And Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

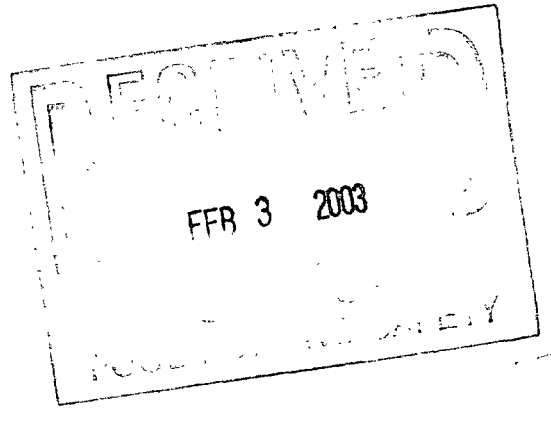
Re: GRAS Notification

Dear Sir or Madam:

In accordance with proposed 21 CFR §170.36 [Notice of a claim for exemption based on a Generally Recognized As Safe (GRAS) determination] published in the Federal Register (62 FR 18939-18964), I am submitting in triplicate, as the notifier, San Joaquin Valley Concentrates, 5631 E. Olive Ave., Fresno, CA 93727, a GRAS notification of grape seed extract (GSE) for use as a natural antioxidant and/or emulsifier in certain conventional foods, a GRAS panel report setting forth the basis for the GRAS determination (as amended), and *curricula vitae* of the members of the GRAS panel for review by the agency.

Please note that, while San Joaquin Valley Concentrates is the notifier of the GRAS exemption claim for GSE, Dry Creek Nutrition, Inc. convened the Expert Panel for the GRAS evaluation. Since the Expert Panel recommendation in November 2001, Dry Creek Nutrition, Inc. merged into San Joaquin Valley Concentrates. Both companies are owned by the same parent company.

Sincerely,



Steven J. Anderson
Vice President

Enclosures

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TOLL FREE:(800)557-0220 OFFICE:(559)458-2500 FAX:(559)458-2564

GRAPE SEED EXTRACT (GSE) NOTIFICATION

GENERALLY RECOGNIZED AS SAFE (GRAS) EXEMPTION CLAIM

Prepared for:

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD
20740-3835

Prepared by:

San Joaquin Valley Concentrates
5631 E. Olive Avenue
Fresno, CA
93727

January 28, 2003

I GRAS Exemption Claim

A. Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997)]

Grape Seed Extract (GSE), as defined in the report in Appendix I entitled, "**EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF GRAPE SEED EXTRACT WITH LESS THAN 5.5% CATECHIN MONOMERS (IH636) FOR USE IN FOODS**", dated November 9, 2001[1], has been determined to be Generally Recognized As Safe (GRAS), consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures as described in the following sections, under the conditions of its intended use in food, among experts qualified by scientific training and expertise. Therefore, the use of GSE in food as described below is exempt from the requirement of premarket approval.

Signed,

1/28/03
Date

Steven J. Anderson
Vice President
San Joaquin Valley Concentrates
5631 E. Olive Ave.
Fresno, CA 93727

B. Name and Address of Notifier

Mr. Steven J. Anderson
Vice President
San Joaquin Valley Concentrates
5631 E. Olive Ave.
Fresno, CA 93727

C. Common Name of the Notified Substance

Grape Seed Extract (GSE)

[1]Dry Creek Nutrition, Inc., convened the Expert Panel for the GRAS evaluation of GSE.

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D. Conditions of Intended Use in Food

GSE is intended for use as a natural antioxidant and/or emulsifier in conventional foods such as beverages and beverage bases, breakfast cereals, fats and oils, frozen dairy desserts and mixes, grain products, milk and milk products, and processed fruits and fruit juices (see Table 1).

Table 1 Summary of the Individual Proposed Food Uses and Use-Levels for Grape Seed Extract (GSE) in the United States

Food Category	Proposed Food Use	Use-Levels for GSE (%)
Beverages and Beverage Bases	Carbonated soft drinks	0.02
Breakfast Cereals	Instant and regular hot cereals	0.08
	Ready-to-eat cereals	0.08
Fats and Oils	Mayonnaise	0.02
Frozen Dairy Desserts and Mixes	Regular and low-fat ice creams and ice milks	0.01
	Frozen yogurt	0.01
Grain Products	Health bars	0.08
Milk, Whole, and Skim	Reduced-fat milks	0.01
Milk Products	Flavored milk based beverages	0.01
	Meal replacements	0.08
	Buttermilk	0.01
	Yogurt	0.02
Processed Fruits and Fruit Juices	Fruit juices	0.02
	Carbonated and fruit-flavored drinks	0.02

Recently, GSE was evaluated by the Flavor and Extract Manufacturers' Association of the United States (FEMA) and was concluded to be acceptable for use as a flavor modifier at levels of 100 to 200 ppm in fruit-based beverages and powdered drink mixes, salad dressings, frozen desserts, cultured dairy products, and skimmed milk (Adams, 2001).

In oil/water systems, GSE functions as a preservative and an emulsifier, while in aqueous solutions, GSE acts as a preservative. The amount used will not be in excess of that necessary to achieve its intended effect as an antioxidant and/or emulsifier, and due to its astringent flavor/taste, the levels of use in conventional food products will not exceed 800 ppm [see Appendix II entitled, "**EXPERT PANEL REPORT CONCERNING THE INCREASED USE LEVELS OF GRAPE SEED EXTRACT WITH LESS THAN 5.5% CATECHIN MONOMERS (IH636) IN FOODS**", dated May 15, 2002].

GSE is a complex mixture of flavonoids composed of 73.32 to 77.63% oligomeric and polymeric flavan-3-ols (proanthocyanidins) and less than 5.5% monomeric flavan-3-ols (catechins) (dry weight basis) (see Section II A). Proanthocyanidins have been identified in various foods

including chocolate, wine, fruits such as apples, cherries and plums, fruit juices, beans, and tea (Macheix *et al.*, 1990; Adamson *et al.*, 1999; Arts *et al.*, 2000a,b; de Pascual-Teresa *et al.*, 2000; Hammerstone *et al.*, 2000; Santos-Buelga and Scalbert, 2000; Scalbert and Williamson, 2000; Teissedre and Landrault, 2000). Based on average values for proanthocyanidin content of different food types (where data exists) and the *per capita* consumption of foods in the United States [U.S. Census Bureau data from USDA, Food Consumption, Prices and Expenditure, 1970-1997], the *per capita* consumption of total proanthocyanidins (including polymers) was conservatively estimated to be 493 mg/day, or 7.04 mg/kg body weight/day for a 70 kg individual (U.S. Department of Commerce, 1999; de Pascual-Teresa *et al.*, 2000; Hammerstone *et al.*, 2000). The estimated average intake of all monomeric flavonoids was reported to be between 23 mg/day (Netherlands) and 170 mg/day (United States) (Hanasaki *et al.*, 1994; Cook and Samman, 1996; Arts *et al.*, 2000a,b).

Using the means of available data of the flavan-3-ol concentration of various foods (Macheix *et al.*, 1990; Vinson *et al.*, 1998; Adamson *et al.*, 1999; Arts *et al.*, 2000a,b; de Pascual-Teresa *et al.*, 2000; Hammerstone *et al.*, 2000; Santos-Buelga and Scalbert, 2000; Scalbert and Williamson, 2000; Teissedre and Landrault, 2000), the *per capita* consumption of monomeric and oligomeric flavan-3-ols in the United States was estimated to be 76 and 147 mg/day, respectively (see Table 2), or 223 mg total flavan-3-ols/day. This value is approximately one half of the estimated total daily proanthocyanidin consumption.

Table 2 Estimated Daily *Per capita* Flavan-3-ol Consumption in the United States

Product	*Per capita* Consumption of Food[1,2]		Average Concentration of Flavan-3-ol[3] (mg/100 g)		Daily *Per capita* Flavan-3-ol Consumption (mg/day)	
	(kg/year)	(kg/day)	Monomers	Oligomers	Monomers	Oligomers
Noncitrus fresh fruit	48.36	0.132	5.3	16.2	7	21
Chocolate	21.90	0.060	49.3	173	30	104
Fruit juice[4]	57.32	0.157	0.8	13.8	1	11
Tea and tea products	31.04	0.085	39.4	6.86	34	6
Wine and wine coolers	11.36	0.031	3.5	7.0	1	2
Beer	128.33	0.352	1.0	0.84	4	3
TOTAL[5]	298.31	0.817	99.56	211.04	76	147

[1] U.S. Department of Commerce (1999)
[2] Seligson *et al.* (1994)
[3] Macheix *et al.* (1990), Vinson *et al.* (1998), Adamson *et al.* (1999), Arts *et al.* (2000a,b), de Pascual-Teresa *et al.* (2000), Hammerstone *et al.* (2000), Santos-Buelga and Scalbert (2000), Scalbert and Williamson (2000), Teissedre and Landrault (2000)
[4] An average proanthocyanidin content for apple, cranberry, and grape juice was calculated from the literature (Arts *et al.*, 2000a,b; Hammerstone *et al.*, 2000; Santos-Buelga and Scalbert, 2000). As citrus products do not contain proanthocyanidins, this value was reduced by 50% to account for orange juice consumption
[5] Other foods known to contain flavan-3-ol proanthocyanidins include some cereal products and various bean varieties; however, these were excluded from the consumption estimate due to lack of consumption or accurate analytical data

The consumption of GSE from all proposed uses was estimated using the United States Department of Agriculture (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (USDA CSFII 1994-1996) and the 1998 Supplemental Children's Survey (USDA CSFII 1998) (USDA, 2000). The mean intake of GSE by the total population that results from the conditions of its intended use in foods was estimated to be 153 mg GSE/person/day, or 2.90 mg/kg body weight/day. The 90th percentile intake of GSE by the total population that results from the conditions of its intended use in foods was estimated to be 291 mg GSE/person/day, or 6.09 mg/kg body weight/day. This level is approximately equivalent to the combined dietary intake of catechin monomers and oligomeric proanthocyanidins from their natural occurrence in food, and less than the total dietary flavan-3-ol consumption.

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E. Basis for the GRAS Determination

The determination that GSE, as defined in Appendix I, is GRAS is on the basis of scientific procedures (see Appendices I and II entitled, "**EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF GRAPE SEED EXTRACT WITH LESS THAN 5.5% CATECHIN MONOMERS (IH636) FOR USE IN FOODS**" and "**EXPERT PANEL REPORT CONCERNING THE INCREASED USE LEVELS OF GRAPE SEED**

EXTRACT WITH LESS THAN 5.5% CATECHIN MONOMERS (IH636) IN FOODS", respectively).

F. Availability of Information

The data and information that serve as the basis for this GRAS notification will be sent to the U.S. Food and Drug Administration (FDA) upon request, or will be available for FDA review and copying at reasonable times at the offices of:

Mr. Steven J. Anderson
Vice President
San Joaquin Valley Concentrates
5631 E. Olive Ave.
Fresno, CA 93727

Should the FDA have any questions or additional information requests regarding this notification, San Joaquin Valley Concentrates will supply these data and information.

II. Detailed Information About the Identity of the Substance

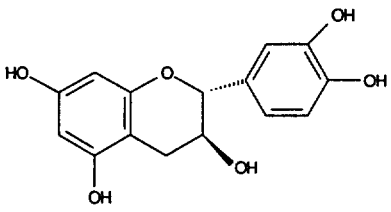
A. Identity

GSE is a natural extract from the seeds of *Vitis vinifera*. It is a rose-brown powder with a tea-like odor and a bitter, astringent taste, and is soluble in water (1.88 g/100 mL water at 50°C). GSE is a complex mixture of monomeric and oligomeric (two to nine monomer units; proanthocyanidins) flavan-3-ols containing trace amounts of lipids and proteins, and small amounts of polysaccharides. The average degree of polymerization of GSE is 5.

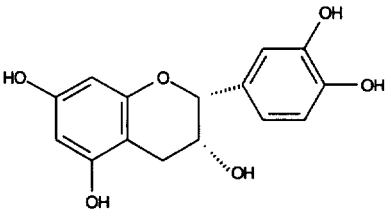
Common or Usual Name:	Grape seed extract (GSE)
Chemical Name:	Proanthocyanidins, rich natural extract
Chemical Abstracts Service (CAS) Number:	Grape seed extract has not been assigned a CAS number

The flavan-3-ols monomers that have been identified in GSE are (+)-catechin, (-)-epicatechin, (-)-epicatechin gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epigallocatechin gallate (EGCG). The structural formulae of the monomeric and oligomeric constituents of HI636 are presented below.

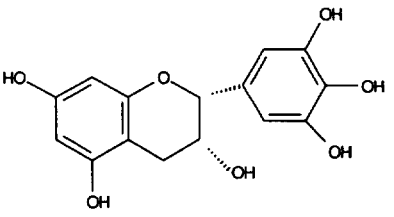
Structural Formulae of Monomeric Constituents:



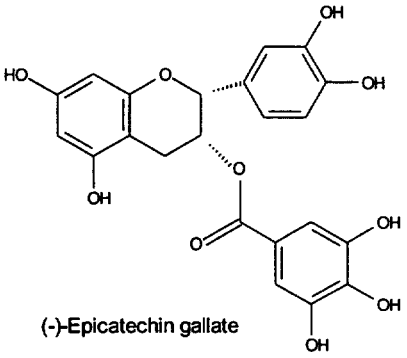
(+)-Catechin



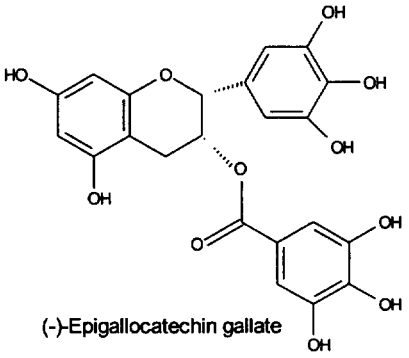
(-)-Epicatechin



(-)-Epigallocatechin

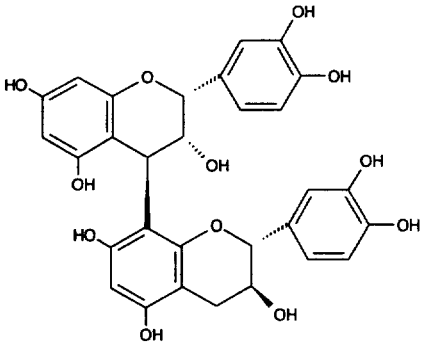


(-)-Epicatechin gallate

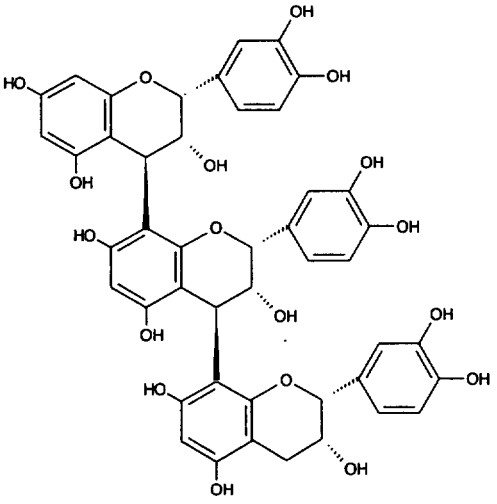


(-)-Epigallocatechin gallate

Structural Formulae of Oligomeric Constituents:



Proanthocyanidin B-1 Dimer



Proanthocyanidin C-1 Trimer

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B. Method of Manufacture

Purified, dried grape seeds are extracted with deionized water under heat and increased pressure and/or reduced oxygen to produce an aqueous proanthocyanidin extract. The aqueous extract is filtered by ultrafiltration to remove suspended solids, adsorbed on a chromatographic column to isolate proanthocyanidins, eluted from the column with ethanol, and concentrated by nanofiltration and/or evaporation. The concentrated extract is dried to remove residual water and ethanol, ground to particle-sized specifications, blended, and packaged in air- and moisture-tight containers. All materials involved in the manufacturing process are appropriate for food use. A schematic diagram of the manufacturing process is presented in Figure 1. Product specifications are presented in Table 3.

Figure 1. Manufacturing Scheme for Grape Seed Extract (GSE)

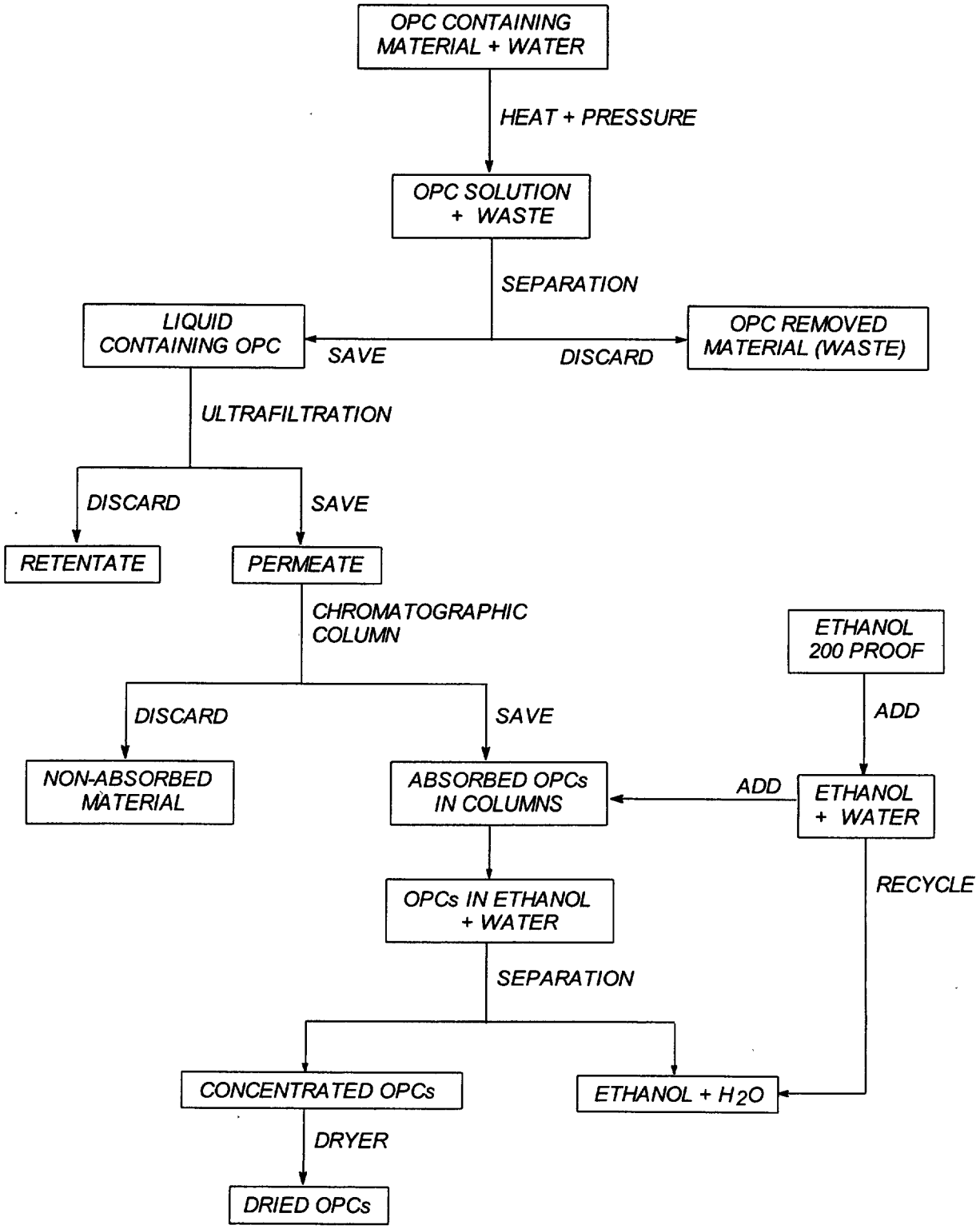

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Table 3 Chemical and Microbiological Specifications for Grape Seed Extract (GSE)	
Specification Parameter	**Specification**
Total phenols (GAE[1], dry basis)	>78%
Total monomers	<5.5%
Loss on Drying (LOD)	<8%
Protein	Not more than 7.0%
Ash	Not more than 1.0%
Fat	Not more than 1.0%
Polysaccharides	Not more than 12%
Heavy metals	
Arsenic	<5 ppm
Mercury	<0.20 ppm
Cadmium	<1.0 ppm
Lead	<1.0 ppm
Microbiological Specifications	
Total plate count	<1,000 cfu[2]/gm
Total Coliform	<3 cfu
Salmonella typhimurium	Negative
Escherichia coli	<3 cfu
Staphylococcus aureus	<10 cfu
Yeast and mold	<100 cfu

[1]Gallic acid equivalents
[2]Colony forming units

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III. Self-Limiting Levels of Use

The levels of use of GSE in foods are limited by its bitter, astringent taste.

IV. Basis for GRAS Determination

Pursuant to 21 CFR §170.30, the grade of GSE intended for use in foods by San Joaquin Valley Concentrates, as defined in Appendix I, has been determined to be GRAS based on scientific procedures. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of GSE as a component of food. The safety of GSE is based on animal and human data, including a subchronic toxicological study on GSE (Wren *et al.*, 2002) and metabolic, mutagenicity, toxicological, clinical, and nutritional studies on other grape seed extract products and/or components of GSE; and supported by a long and safe history of proanthocyanidin consumption as a result of their abundant natural presence in food; and the small quantities expected to be consumed from the proposed uses. This determination is further supported by an Expert Panel evaluation of the health aspects of GSE, other grape seed extract products, and components thereof (see Appendix I).

As specified in Appendix I, the potential genotoxicity of proanthocyanidin monomers, oligomers, and polymers has been evaluated in various mutagenicity and genotoxicity assays. Evidence of toxicity or mutagenicity was reported not to occur when these compounds were tested in the Ames assay, with or without metabolic activation (Brown and Dietrich, 1979; Yu and Swaminathan, 1987; Takahashi *et al.*, 1999; Duarte Silva *et al.*, 2000). Overall, monomeric and oligomeric constituents of grape seed extract did not produce mutagenic effects or induce DNA damage in the sister chromatid exchange assay or the chromosomal aberration assay (Jain and Sethi, 1991; Popp and Schimmer, 1991; Takahashi *et al.*, 1999; Duarte Silva *et al.*, 2000). Takahashi *et al.* (1999) reported the production of polyploidy in Chinese hamster lung (CHL) cells by the proanthocyanidin B-2 dimer both in the absence (~12%) and presence (~20%) of metabolic activation; however, no structural aberrations were induced. Alternatively, the B-2 dimer did not induce polyploidy in human lymphocyte cultures (Popp and Schimmer, 1991), and negative results were reported for the B-2 dimer *in vivo* in the micronucleus test in mice (Takahashi *et al.*, 1999). It was concluded by Takahashi *et al.* (1999) that the proanthocyanidin B-2 dimer "induced only polyploidy in chromosomal aberration tests *in vitro*." In subsequent mutagenicity and genotoxicity tests of a grape seed extract with a similar composition to GSE (Gravinol Super™) (see Appendix III entitled, "**COMPARISON OF THE OLIGOMERIC AND MONOMERIC FLAVAN-3-OL DISTRIBUTION IN TWO COMMERCIAL GRAPE SEED EXTRACT PREPARATIONS**"), mutagenicity was reported not to occur *in vitro* in the Ames assay using *Salmonella typhimurium* or in the chromosomal aberration assay using CHL cells, both with and without metabolic activation (Yamakoshi *et al.*, 2002a). Although the authors reported the proanthocyanidin dimers and tetramers to exhibit "weak activities", which they

suggested were possibly the result of rapid autoxidation of the proanthocyanidins under the alkaline conditions, aneuploidy and polyploidy were not induced by proanthocyanidin dimers, trimers, or tetramers in the *in vitro* chromosomal aberration test. Negative results were reported *in vivo* in the micronucleus test in mice (Yamakoshi *et al.*, 2002a; Erexson, 2003), which the authors considered to be strong support for the lack of mutagenic and clastogenic activity of grape seed extract.

Evaluation of scientific data pertaining to the possible health effects of GSE under the intended conditions of use in foods by the Expert Panel resulted in the conclusion that GSE, "meeting food grade specifications and produced in compliance with cGMP (current good manufacturing practice), is Generally Recognized As Safe (GRAS) by scientific procedures for use as an antioxidant and/or emulsifier in conventional foods under the conditions of intended use described herein" (see Appendix I). Subsequent to the GRAS evaluation, additional feeding studies of the potential toxicological effects of grape seed extracts of similar composition [*i.e.*, Gravinol Super™; 89.3% (w/w) oligomers and polymers, 6.6% monomers (w/w) (see Appendix III)] to GSE have been made publicly available (Bentivegna and Whitney, 2002; Yamakoshi *et al.*, 2002a). The results of these studies indicated that, grape seed extract, administered to rats *via* the diet at levels providing up to 1,780 mg/kg body weight/day in males and 2,150 mg/kg body weight/day in females, did not produce adverse effects, and thus support the safe use of proanthocyanidin-rich extracts as dietary components for human consumption. In addition, various clinical, non-clinical, and *in vitro* studies have been conducted to investigate the possible beneficial effects of dietary grape seed extract as a biological antioxidant (Shao *et al.*, 2001; Kalin *et al.*, 2002; Khanna *et al.*, 2002; Natella *et al.*, 2002; Pataki *et al.*, 2002; Shanmuganayagam *et al.*, 2002; Vinson *et al.*, 2002; Yamakoshi *et al.*, 2002b).

Chemical analysis of GSE indicated the presence of trace amounts of quercetin (0.11 mg/g GSE). Quercetin is a member of the flavonol class of flavonoids, and has been reported to occur naturally in various fruits and vegetables including onions, kale, beans, apples, and cherries (Hertog *et al.*, 1992). The daily intake of quercetin from its natural occurrence in the diet was reported to range from 2.6 to 38.2 mg/person, with an average intake of approximately 16 mg quercetin/person/day (Hertog *et al.*, 1993; 1995; Arai *et al.*, 2000). With an estimated total population 90th percentile intake of 291 mg GSE/person/day from its intended use in foods, the level of intake of quercetin is expected to be not more than 0.032 mg/person/day. This level is approximately 500 times less than the average dietary intake of quercetin, and thus is expected not to produce adverse effects on human health.

V. References

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Appendix I

APPENDIX I

EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF GRAPE SEED EXTRACT WITH LESS THAN 5.5% CATECHIN MONOMERS (IH636) FOR USE IN FOODS

EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF GRAPE SEED EXTRACT WITH LESS THAN 5.5% CATECHIN MONOMERS (IH636) FOR USE IN FOODS

November 9, 2001

Introduction

As independent experts qualified by relevant national and international experience and scientific training to evaluate the safety of food ingredients, we, the undersigned, Joseph F. Borzelleca, Ph.D. (Medical College of Virginia), Andrew L. Waterhouse, Ph.D. (University of California), and Gary Williams, M.D. (New York Medical College), were requested by the manufacturer, Dry Creek Nutrition, Inc., as an Expert Panel (hereinafter referred to as the Panel) to evaluate the safety and to determine the Generally Recognized As Safe (GRAS) status of Grape Seed Extract with less than 5.5% Catechin Monomers (IH636) under the conditions of intended use in conventional foods as an antioxidant and/or emulsifier. *Curricula vitae* evidencing the qualifications of the Panel for evaluating the safety of food ingredients are provided in Attachment 1.

The Panel, independently and collectively, critically examined a comprehensive package of publicly available scientific information and data compiled from the literature and other published sources. In addition, the Panel evaluated other information deemed appropriate or necessary, including data and information provided by Dry Creek Nutrition Inc. The data evaluated by the Panel included information pertaining to the method of manufacture and product specifications, analytical data, the intended use of IH636 as an antioxidant and/or emulsifier, exposure data, and comprehensive literature on the safety of grape seed extract components and studies on IH636.

Following independent and collective critical evaluation of available data and information summarized herein, the Panel was asked to render an opinion on whether IH636, meeting appropriate food grade specifications and manufactured in compliance with current Good Manufacturing Practices, is Generally Recognized As Safe (GRAS) based on scientific procedures.

Composition, Manufacturing and Specifications

IH636 is a natural extract from the seeds of *Vitis vinifera*. It is a complex mixture of monomeric and oligomeric flavan-3-ols (two to nine monomer units) (proanthocyanidins) containing trace amounts of lipids and proteins, and small amounts of polysaccharides. The flavan-3-ols that have been identified in IH636 are (+)-catechin, (-)-epicatechin, (-)-epicatechin gallate, (-)-epigallocatechin, and (-)-epigallocatechin gallate.

Purified, dried grape seeds are extracted with deionized water under heat and increased pressure and/or reduced oxygen to produce an aqueous proanthocyanidin solution. The aqueous solution is purified by ultrafiltration, and elution from an adsorption resin with ethanol, and concentrated by nanofiltration. The extract is dried to remove residual water and solvent, ground to particle-sized specifications, blended, and packaged in an air-and moisture-tight container. All materials involved in the manufacturing process are appropriate for food use. Product specifications are presented in Table 1.

Regulatory Status

IH636 is marketed as a dietary supplement in the United States under the Dietary Supplements Health and Education Act. Two similar proanthocyanidin containing extracts, grape color extract (21 CFR §73.169) used in non-beverage foods and grape skin extract (21 CFR §73.170) used in beverages, are permitted color additives (CFR, 2001c). Recently, IH636 was evaluated by the Flavor and Extract Manufacturer's Association and was found to be acceptable for use as a flavoring agent at levels of 100 to 200 ppm in fruit based beverages, powdered drink mixes, salad dressings, frozen desserts, cultured dairy products, and skimmed milk.

Intended Use

IH636 is intended to be used as an antioxidant and/or emulsifier in conventional foods such as beverages and beverage bases, breakfast cereals, fats and oils, frozen dairy desserts and mixes, grain products, milk and milk products and processed fruits and fruit juices. It acts as a preservative in a number of aqueous and oil/water systems and as an emulsifier in oil/water systems. The levels of use are self-limiting as a result of its astringent flavor/taste at use levels > 500 ppm. Intended food uses and use levels are presented in Table 2. IH636 is not intended for use in foods consumed by infants.

Exposure Estimates

Proanthocyanidins occur naturally in foods such as tea, chocolate, wine, and fruits, and the *per capita* consumption of proanthocyanidins from these foods was estimated to be 493 mg/day, or 7.04 mg/kg body weight/day for a 70 kg individual.

The consumption of IH636 from all proposed uses was estimated using the United States Department of Agriculture (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (USDA CSFII 1994-1996) and the 1998 Supplemental Children's Survey (USDA CSF II 1998) (USDA, 2000). The mean and 90th percentile intake of IH636 by the total population from all proposed food-uses was estimated to be 138 mg/person/day (2.58 mg/kg body weight/day) and 264 mg/person/day (5.46 mg/kg body weight/day).

Data Pertaining to Safety

The safety of IH636 is based on (a) a history of proanthocyanidin consumption as a result of their abundant natural presence in food, (b) the small quantities expected to be consumed from proposed uses, (c) toxicological and clinical studies on IH636, and (d) metabolic, mutagenicity, toxicological, clinical, and nutritional studies on components of IH636.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Generally, oligomeric proanthocyanidins are poorly absorbed across the intestinal lumen, although it has been reported that oligomeric proanthocyanidins may be hydrolyzed to monomers, dimers, and trimers in an acidic environment, such as stomach and upper intestinal tract (Spencer *et al.*, 2000). These dimers and trimers may be absorbed intact or further degraded to flavan-3-ol monomers in the intestinal lumen. Monomers may be absorbed across the intestinal lumen intact or partially metabolized by the intestinal microflora to phenylvalerolactones, and to a certain extent further to phenolic acids and their derivatives. Following absorption, proanthocyanidins are transported to the liver *via* the portal system, where they form glucuronide and/or sulfate or methyl conjugates. Proanthocyanidins also may be distributed to other tissues such as the kidney, lung, spleen, and connective tissue. Catechin metabolites, such as the phenylvalerolactones, are *O*-methylated in the intestinal cell. The acids are further oxidized by β-oxidation to benzoic acid derivatives, which may further be conjugated with glycine to hippuric acid derivatives. Proanthocyanidins and their metabolites are eliminated through urinary, fecal, and biliary excretion, and *via* respired carbon dioxide.

Toxicological Studies

Acute Studies

LD_{50} values of greater than 5 g/kg body weight obtained in acute studies indicate that grape seed extract and (+)-catechin have low oral toxicity in various laboratory animals such as mice, rats and dogs (Unno *et al.*, 1982; Varsho, 1996; Yamane *et al.*, 1996; Bagchi *et al.*, 2000).

Subchronic and chronic studies

Two oral toxicity studies have been performed using IH636. In a 90-day oral toxicity study, IH636 was provided to 4 groups Sprague-Dawley rats (20 rats/sex/group) at levels of 0, 0.5, 1.0, or 2.0% (Wren *et al.*, 2001). On a body weight basis, these doses were reported to be equivalent to 0, 348, 642, and 1,586 mg/kg body weight, respectively, for male rats, and 0, 469, 883, and 1,928 mg/kg body weight, respectively, for female rats. The authors reported no compound-related effects on body or organ weights, ophthalmology evaluation, or clinical chemistry or histopathological parameters in any of the animals. Decreased serum iron levels were reported in male rats in the high-dose group; however, the authors reported these levels to be within range of historical limits (Loeb and Quimby, 1989; Wren *et al.*, 2001). A significant

increase in food consumption was reported in male rats in the high-dose group absent of accompanying gains in body and absolute organ weights. No adverse effects were observed at 2.0% in the diet, the highest dose tested.

Male B6C3F1 mice were provided IH636 in the diet at levels designed to deliver 0 or 100 mg/kg body weight/day for a period of 12 months (Ray and Bagchi, 2000). No compound-related deaths or effects on body weight gains, or macroscopic or histopathological changes in any of the organs of the treated animals were reported.

Additional oral toxicity studies have been performed using similar extracts from grape seeds. Six groups of adult male ICR (CD-1) mice (number of animals/group not specified), were administered 100 mg grape seed extract/kg body weight by gavage for periods up to 7 to10 days (Bagchi *et al.*, 2001). No significant changes were reported in serum alanine aminotransferase (ALT) and creatine kinase activity, blood urea nitrogen level, organ histopathology, or DNA fragmentation compared to the saline control groups. No other parameters were evaluated.

Groups of 52 weanling Brown Norway/Fischer 344 hybrid rats (BN/F344) were provided a basal diet containing 0 or niacin-bound chromium (providing approximately 5 ppm chromium), zinc monomethionine (providing 18 ppm zinc), and 250 ppm grape seed extract for a period of 10 months to 1 year (Preuss *et al.*, 2001). Using an estimate of 1 ppm equivalent to 0.05 to 0.1 mg/kg body weight/day (U.S. FDA, 1993), this would correspond to a level of approximately 12.5 to 25 mg grape seed extract/kg body weight/day. Body and organ weights, blood chemistry, TBARS, and SBP were obtained for both groups, and the activity of the renin-angiotensin and nitric oxide systems of the rats was assessed. The authors reported no evidence of toxicity.

Various studies in rats and dogs have investigated the possible effects of subchronic administration of monomeric catechin fractions of tea. No relevant toxicological effects were noted at levels up to 150 mg/kg body weight/day over 28 days. Kao *et al.* (2000) examined the possible physiological effects of orally and intraperitoneally administered green tea catechins in male and female Sprague-Dawley and lean and obese male Zucker rats. Male and female Sprague-Dawley rats were provided 0 or 15 mg epigallocatechin gallate in the diet for a period of 7 days. Additionally, dose-dependent effects were evaluated following intraperitoneal injections of 0 or 26 to 92 mg catechin monomers/kg body weight to male and female Sprague-Dawley rats for a period of 7 days, and 81 or 92 mg epigallocatechin gallate/kg body weight to lean and obese Zucker rats, respectively. The authors reported dose-dependent decreases in body weight gains that resulted from decreased food intake in male and female Sprague-Dawley rats administered epigallocatechin gallate, but not epigallocatechin or other catechins. The decreased weight gains were accompanied by decreased weights of accessory sexual organs, liver, kidney, testes, and spleen in Sprague-Dawley and lean Zucker rats, but not in obese Zucker rats. Epigallocatechin gallate was reported not to be toxic to the liver or kidney and did not produce changes in serum enzymes.

For a period of 28 days, 15 or 75 mg/kg body weight green tea extract containing (+)-catechin, epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate were provided orally to Sprague-Dawley rats (method of oral administration (diet, water, gavage) not specified) (Yamane *et al.*, 1996). The green tea extract was reported not to affect body weight gains or hematological or biochemical parameters. As reported in a published summary of a preclinical trial sponsored by the Chemoprevention Branch, dogs (1/sex/group) were orally administered 20, 75 or 150 mg epigallocatechin gallate (capsule form)/kg body weight/day for a period of 28 days (NCI, 1996). Due to a lack of observed toxicity in dogs in the low-dose group (20 mg/kg body weight/day), the animals were administered 300 mg epigallocatechin gallate/kg body weight/day for the remaining 2 weeks of the study period. The authors reported that oral administration of epigallocatechin gallate produced no compound-related toxicity.

Reproductive and Developmental Studies

The possible effects of (+)-catechin on reproductive and developmental parameters were examined by Mitsumori *et al.* (1982a) in a 3-generation rat study. (+)-Catechin was administered orally (method of oral administration not specified) to groups of 21, 21, 22, or 29 pregnant Sprague-Dawley rats at levels of 0 (control), 450, 1,500, and 5,000 mg/kg body weight/day, respectively from Day 7 to Day 17 of gestation (Japanese article, English summary and tables only). Laparotomy of approximately two-thirds of the dams in each group was performed on Day 21 of gestation for examination of the F_1 fetuses. The remaining dams were allowed to deliver naturally. Dams administered 5,000 mg/kg body weight/day were reported to have decreased body weight gains and food intake, and increased water intake compared to controls. At necropsy, the dams in the 5,000 mg/kg body weight/day dose group were reported to have lower liver weights and enlarged caecum relative to the control group. No effects were reported in the other treatment groups. Slightly lower body weights and retarded development of the caudal vertebrae of male F_1 fetuses examined on Day 21 of gestation were reported when compared to the controls, and the authors reported this difference to be statistically significant. No other effects on the F_1 fetuses were reported. No significant differences in the post-natal development between the F_1 pups and controls were reported. Compared to controls, relative weights of the heart of males and the uterus of females in the 1,500 mg/kg body weight dose groups were decreased, and the relative weights of the lung and ovary of females in the 5,000 mg/kg body weight/day dose group were increased. The authors reported no compound-related effects on the reproductive abilities of the F_1 generation, and no developmental effects in the F_2 generation. The authors reported a maximum safe dose of 1,500 mg/kg body weight/day for pregnant rats and fetuses.

In a study designed to investigate the potential peri- and postnatal effects of flavanols, (+)-catechin was administered orally (method of administration not specified) to groups of pregnant Sprague-Dawley rats (24 rats/group) at levels of 0 (control), 450, 1,500, and 5,000 mg/kg body weight/day from Day 17 of gestation to Day 21 of lactation (26 days total), at which time the dams were necropsied (Japanese article, English summary and tables only) (Mitsumori

et al., 1982b). Body weight gains and food intake of dams in the 1,500 and 5,000 mg/kg body weight/day dose groups were reported to be decreased during gestation, and water intake was increased during lactation compared to controls. Some significant differences in relative organ weights of the dams were reported. The relative liver weights of dams in the 1,500 and 5,000 mg/kg body weight/day and kidney weights in the 450 and 5,000 mg/kg body weight/day dose groups were increased compared to controls; however, the authors reported that these differences were not of toxicological significance, and these effects were not reported at these doses in dams in the developmental study. Measurement of body weight gain, viability, general behavior, sensory functions, open-field behavior, and learning ability was reported not to show any compound-related effects in the F_1 pups. Relative weights of the thymus of males and uterus of females in the 5,000 and 450 mg/kg body weight/day dose groups, respectively, were reported to be increased compared to controls. No significant differences in the reproductive ability of the F_1 generation or developmental effects in the F_2 generation rats were reported, and the authors reported a maximum safe dose for peri- and postnatal pups of 5,000 mg/kg body weight/day.

Oral administration of 0 (control), 125, 250, or 500 mg (+)-catechin/kg body weight/day to pregnant New Zealand White rabbits on Days 6 to 18 of gestation was reported not to result in any embryotoxic or teratogenic effects in any of the fetuses (Yokoi *et al.*, 1982).

Other Studies

Several studies designed to examine the possible oncoprotective properties of proanthocyanidins against several carcinogens, such as 7,12-dimethyl-benz[a]anthracene (DMBA), 1,2-dimethylhydrazine (DMH), or 2,2'-dihydroxy-di-n-propylnitrosamine (DHPN), have provided details of control groups Sprague-Dawley or F344 rats administered catechin monomers only at oral dose levels up to 1,000 mg/kg body weight/day for periods of 23 to 33 weeks (Hirose *et al.*, 1993, 1997, 2001). No proanthocyanidin-related adverse effects on body weight gains or final organ weights were reported. Additionally, proanthocyanidins were reported not to adversely affect the progression, incidence, or multiplicity of carcinogen-induced tumorigenesis.

Genotoxicity Studies

The genotoxic potential of proanthocyanidin polymers, oligomers, and monomers were evaluated in the Ames assay using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 and in a strain of *Escherichia coli* (WP2uvrA). No evidence of toxicity or mutagenicity was reported at concentrations of up to 5 mg/plate (the highest concentration used), with or without metabolic activation (Brown and Dietrich, 1979; Yu and Swaminathan, 1987; Takahashi *et al.*, 1999; Duarte Silva *et al.*, 2000). Overall results of the sister chromatid and the chromosomal aberration assays using human lymphocyte and Chinese hamster lung cells indicated that the oligomeric and monomeric constituents of grape seed extract do not

produce mutagenic effects or induce DNA damage (Jain and Sethi, 1991; Popp and Schimmer, 1991; Takahashi *et al.*, 1999; Duarte Silva et al., 2000). The proanthocyanidin B-2 dimer was reported to produce polyploidy in Chinese hamster lung (CHL) cells in the absence (~12%) and presence (~20%) of metabolic activation (Takahashi *et al.*, 1999); however, Popp and Schimmer (1991) reported that the B-2 dimer did not induce polyploidy in human lymphocyte cultures and Takahashi *et al.* (1999) reported negative results for the B-2 *in vivo* in the micronucleus test in mice. Takahashi *et al.* (1999) concluded that proanthocyanidin B-2 dimer "induced only polyploidy in chromosomal aberration tests *in vitro*."

Clinical Studies Relating to the Safety of Grape Seed Extract

Various short-term clinical trials and epidemiological studies of grape seed extract proanthocyanidins and/or monomeric constituents have been performed to elucidate their metabolic profile and possible heath benefits, such as antioxidant capabilities, cardioprotective, and anticarcinogenic effects. Although not performed as safety assessments, these studies resulted in no adverse effects at doses in the range or in excess of the estimated intake level, and thus provide evidence for the safety of proanthocyanidins.

No adverse effects were reported in several longer term feeding trials with tea catechins at doses in excess of the estimated intake levels. A group of 30 healthy volunteers with slightly more females than males (exact numbers not reported), 20 to 70 years of age, were provided 500 mg tea catechins daily in tablet form (two 250 mg catechin tablets/day) for a period of 3 months (approximately 8 mg/kg body weight/day for a 60 kg individual) (Hara, 1997). Approximately 11 to 38% of the volunteers reported improvements in bowel movements, stool condition, and overall health general condition. During and after the 3-month study period, no abnormalities in body weight, blood pressure, clinical chemistry, or general clinical examinations were reported. Similar results were reported by Yamane *et al.* (1996) in a study in which 20 healthy volunteers (10 males, 10 females) received 1 g green tea extract/day in tablet form. In 15 tube-fed patients (5 males, 10 females) provided 300 mg tea catechins/day, measurements on fecal flora were reported to indicate increased lactic acid-producing bacteria, decreased putrefactive bacteria, and a lowered intestinal pH (Hara, 1997). A summary of the prospective clinical trials and epidemiological studies of grape seed extract proanthocyanidins and monomeric constituent is presented in Table 3.

The Panel noted that (+)-catechin (Catergen) was approved in Europe for use as a drug in the 1970's for treatment of patients with acute or chronic viral hepatitis. Identified case reports indicated that the treatment regimen included doses of 1,500 to 2,250 mg/person/day for periods of up to 24 weeks (Kanai, 1988; Suzuki, 1986; Rotoli *et al.*, 1985). Reported Adverse Drug Reactions (ADR), such as fever, skin reactions, hemolytic anemia, and death, resulted in suspension of Catergen as a drug in 1986. The estimated exposure of (+)-catechin from the intended uses of IH636 for a heavy user is expected to be approximately 4 mg (+)-catechin/person/day. The exposure to (+)-catechin from IH636 is well below the doses of

Catergen that were reported to produce ADR and lower than that consumed from the diet (Kühanu, 1976; Scalbert and Williamson, 2000; Macheix *et al.*, 1990). Therefore, the exposure to (+)-catechin from the intended uses of IH636 would not be expected to produce adverse health effects in humans.

Nutritional Studies

Possible Effects of Plant Polyphenols or Tannins on Non-heme Iron Absorption

Iron absorption has been reported to be affected by the formation of iron complexes within the intestinal lumen. Several studies have indicated that non-heme iron absorption may be inhibited by plant polyphenols, especially catechin monomers contained in foods such as tea (South *et al.*, 1997; Disler *et al.*, 1995; Cooke *et al.*, 1995). In an effort to identify the relative inhibitory effect with different polyphenol structures, Brune *et al.* (1989) measured iron absorption in subjects provided a bread meal, to which was added equivalent amounts of a variety of phenolic acids, (+)-catechin, and tannic acid as a model for polymeric structure. Gallic acid, in amounts naturally present in the diet, was reported to reduce iron absorption by ~50% compared with 30% for chlorogenic acid (found in coffee) and no effect at all with (+)-catechin. Tannic acid, containing 10 gallic acid residues, caused a dose-dependent decrease of iron absorption (88% reduction with 100 mg tannic acid). This was equivalent to its gallic acid content. Oregano and tea also inhibited iron absorption in proportion to their galloyl groups. The authors concluded that the content of iron-binding galloyl groups might be a major determinant of the inhibitory effect of polyphenolic compounds on iron absorption from the diet. The authors further suggested that the flavanols, both catechins and the oligomeric proanthocyanidins, did not interfere with iron absorption.

In male, but not female rats, provided IH636 in the diet at levels of up to 2.0% for a period of 90 days, decreased serum iron levels were reported in the highest dose group; however, authors reported these levels to be within range of historical limits (Wren *et al.*, 2001). Although available scientific evidence indicates that gallic acid esters of dietary polyphenols are responsible for binding iron in the gut preventing iron absorption, only 10% of IH636 contains proanthocyanidins esterified to gallic acid (approximately 13 mg/day) that could contribute to inhibition of iron absorption from the diet (Dry Creek Nutrition, Inc., personal communication; Brune *et al.*, 1989). This amount is far less than the proanthocyanidins consumed by eating an apple, drinking a glass of red wine, or eating 20 g of dark chocolate (Scalbert and Williamson, 2000). Many other factors have significant effects on gastro-intestinal iron absorption and the overall absorption of iron from a complete meal is a result of the contribution of each active chemical within that meal. Ascorbic acid, meat, fruits, and fruit juices enhance iron absorption, whereas polyphenols in tea and coffee will inhibit iron absorption as will phytate in bran and rye bread, calcium in milk and cheese and soy protein.

Possible Effects of Proanthocyanidins on Protein Absorption

Antinutritional effects of proanthocyanidins, such as decreased body weight gains, lower food and protein efficiency, inhibition of digestive enzyme systems, and increased fecal nitrogen, have been reported by various authors (Shahkhalili *et al.*, 1990; Butler, 1992; Tebib *et al.*, 1995; Chung *et al.*, 1998). Tannins, both condensed (proanthocyanidins) and hydrolysable, have an affinity for binding proteins, which may result in a lower digestibility of dietary proteins in a dose-dependent manner (Ricardo da Silva *et al.*, 1991a; Vallet *et al.*, 1994; Santos-Buelga and Scalbert, 2000).

Alkaline phophatase (AP) activity was inhibited in an *in vitro* system by grape seed extract proanthocyanidins; however, addition of biliary juice to the incubation medium was reported to decrease or prevent inhibition of enzyme activity (Tebib *et al.*, 1995). In two studies designed to investigate the possible effects of grape seed condensed tannins on the activity of rat intestinal enzyme activities, 2 to 3 groups of 6 male Sprague-Dawley rats were provided diets containing up to 2.0% grape seed extract proanthocyanidins for a period of 31 days (approximately 1,000 mg/kg body weight/day) (U.S. FDA, 1993; Vallet *et al.*, 1994; Tebib *et al.*, 1995). In both studies, rats receiving the grape seed tannins-containing diet were reported to have decreased body weight gains and increased fecal dry weight compared to the control group. Tebib *et al.* (1995) reported that the grape seed extract proanthocyanidin-diets inhibited AP activity in the jejunum, and sucrase and dipeptidyl peptidase IV activity in the ileum of rats, whereas, Vallet *et al.* (1994) reportedly observed no significant effects on AP activity.

The dose-dependent effects of the protein binding affinity of proanthocyanidins are clearly demonstrated in feeding studies in rats (Vallet *et al.*, 1994; Tebib *et al.*, 1995; 1996). Consumption of levels of up to 100 mg grape seed monomers or polymers/kg body weight were reported not to produce adverse effects for a period of up to 12 weeks, while consumption of much higher levels (at least 1,000 mg/kg body weight) was reported to result in decreased body weight gains and increased fecal nitrogen. Numerous proteins are present in the digestive tract that may competitively bind proanthocyanidins, and the effect on digestive enzymes was proposed to be lessened in the presence of other dietary proteins (Butler, 1992; Santos-Buelga and Scalbert, 2000). Others have suggested that the increased fecal nitrogen is instead endogenous protein from the lining and secretions of the digestive tract, including proline-rich salivary proteins (Shahkhalili *et al.*, 1990; Butler, 1992; Helsper *et al.*, 1993). Proline-rich salivary proteins have a high affinity for proanthocyanidins and the secretion of proline-rich salivary proteins may counteract the biological action of complexation of proanthocyanidins with dietary proteins (Ricardo da Silva *et al.*, 1991a).

IH636 fed to Sprague-Dawley rats at a level up to 2% of the diet for 90 days resulted in a significant increase in food consumption in male rats in the high-dose group absent of accompanying gains in body and absolute organ weights, or histopathological effects. Considering that rats normally eat to a constant energy level, the high dose male rats appear to

have less access to available energy, suggesting that IH636 may interfere with nutrient digestion at dosages far in excess of proposed uses.

Summary

Overall, when viewed in its entirety, the scientific evidence for proanthocyanidins and their monomeric constituents support the safe intake of IH636 by humans. Existing animal studies with proanthocyanidin oligomers and monomers do not indicate adverse reproductive or developmental effects in humans from dietary exposure at the intended levels of use.

The Panel noted the possible nutritional effects of proanthocyanidins on iron and protein absorption. Results from a 90-day feeding study in rats of IH636 at levels of 0, 0.5, 1.0, or 2.0% (Wren *et al.*, 2001) indicated decreased serum iron levels and a significant increase in food consumption absent of accompanying gains in body and absolute organ weights in male rats in the high-dose group, which may have been related to the potential nutritional effects of proanthocyanidins. However, no effects were observed in rats consuming IH636 at a level of 1.0% in the diet. The Panel considered that the serum iron levels to be within range of historical limits and the potential effects on protein or energy availability, biologically insignificant at proposed levels of consumption. No other significant compound-related adverse effects from dietary exposure to proanthocyanidins or their monomeric constituents have been reported.

Prospective clinical trials and epidemiological studies as well as reported dietary intervention studies using levels of grape seed extract proanthocyanidins or their monomeric constituents that are similar to, or greater than, the estimated intake from the intended food uses of IH636, indicate that these levels are well-tolerated by humans, and are without reported adverse effects.

The Panel also was aware of the recommendation to the National Toxicology Program (NTP) for testing of grape seed extract and epigallocatechin gallate because of their use as dietary supplements and potential as cancer chemopreventive agents. Comments on the nomination for testing of these substances have not yet been published.

Conclusion

We, the Expert Panel, have independently and collectively critically evaluated the data and information summarized above and conclude that Grape Seed Extract with less than 5.5% Catechin Monomers, meeting food grade specifications and produced in compliance with cGMP, is Generally Recognized As Safe (GRAS) by scientific procedures for use as an antioxidant and/or emulsifier in conventional foods under the conditions of intended use described herein.

09 November 2001
Date

Joseph Borzelleca, Ph.D.
Professor, Pharmacology and
Toxicology
Medical College of Virginia
Virginia Commonwealth University

9 November, 2001
Date

Andrew Waterhouse, Ph.D.
Professor of Enology
Department of Viticulture and
Enology
University of California

09 Nov 01
Date

Gary Williams, M.D.
Professor of Pathology
Department of Pathology
New York Medical College

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Table 1 Chemical and Microbiological Specifications for Grape Seed Extract with less than 5.5% Catechin Monomers	
Specification Parameter	**Specification**
Total phenols (GAE[1], dry basis)	>78%
Total monomers	<5.5%
Loss on Drying (LOD)	<8%
Protein	Not more than 7.0%
Ash	Not more than 1.0%
Fat	Not more than 1.0%
Polysaccharides	Not more than 12%
Heavy metals	
Arsenic	<5 ppm
Mercury	<0.20 ppm
Cadmium	<1.0 ppm
Lead	<1.0 ppm
Microbiological Specifications	
Total plate count	<1,000 cfu[2]/gm
Total Coliform	<3 cfu
Salmonella typhimurium	Negative
Escherichia coli	<3 cfu
Staphylococcus aureus	<10 cfu
Yeast and mold	<100 cfu

[1] Gallic acid equivalents
[2] Colony forming units

Table 2 Summary of the Individual Proposed Food Uses and Use-Levels for Grape Seed Extract with less than 5.5% Catechin Monomers in the U.S.		
Food Category	**Proposed Food Use**	**Use-Levels for Grape Seed Extract with less than 5.5% Catechin Monomers (%)**
Beverages and Beverage Bases	Carbonated soft drinks	0.02
Breakfast Cereals	Instant and regular hot cereals	0.04
	Ready-to-eat cereals	0.04
Fats and Oils	Mayonnaise	0.02
Frozen Dairy Desserts and Mixes	Regular and low-fat ice creams and ice milks	0.01
	Frozen yogurt	0.01
Grain Products	Health bars	0.04
Milk, Whole, and Skim	Reduced-fat milks	0.01
Milk Products	Flavored milk based beverages	0.01
	Meal replacements	0.04
	Buttermilk	0.01
	Yogurt	0.02
Processed Fruits and Fruit Juices	Fruit juices	0.02
	Carbonated and fruit-flavored drinks	0.02

Table 3 Grape Seed Extract and Monomeric Constituent Intakes of Subjects in Prospective Clinical Trials and Epidemiological Studies

Number of Subjects	Source of Monomers and/or Polymers	Exposure Period	Estimated Intake of Catechin Monomers (mg/person/day)	Measured Outcome	Reference
Safety Studies					
15 tube-fed fecal metabolic patients	Green tea catechin	3 weeks	300 mg total catechins	↑ lactic acid bacteria and organic compounds ↓ putrefactive bacteria and odorous compounds and a lowered pH	Hara, 1997
23 healthy volunteers	Sugar-free green tea chew candies	4 weeks	~350 to 485 mg total catechins	No adverse effects Slight ↓ in gingival inflammation	Krahwinkel and Willershausen, 2000
30 healthy volunteers	Green tea catechins in tablet form	3 months	500 mg total catechins	No adverse effects	Hara, 1997
20 healthy volunteers	Green tea extract in tablet form (1 g)	3 months	~745 mg total catechins	No adverse effects	Yamane *et al.*, 1996
Absorption, Distribution, Metabolism, and Excretion (ADME) Studies					
3 healthy males	(+)-Catechin capsules (500 mg)	Single dose	2,000	Urinary excretion of (+)-catechin and metabolites (55%) ↑ plasma concentration of unchanged (+)-catechin	Hackett *et al.*, 1983
6 healthy males	(+)-Catechin granules suspended in water	Single dose[1]	500, 1,000, and 2,000	Unchanged (+)-catechin and metabolites in serum	Balant *et al.*, 1979
4 healthy subjects	Green tea powder	Single dose	~100[2] EGC	↑ serum level of EGCG	Unno *et al.*, 1996
18 healthy subjects	Decaffeinated green tea extract	Single dose	282, 564, or 846 total catechin[3]	↑ plasma level of EGCG, EGC, and EC	Yang *et al.*, 1998

Table 3 Grape Seed Extract and Monomeric Constituent Intakes of Subjects in Prospective Clinical Trials and Epidemiological Studies

Number of Subjects	Source of Monomers and/or Polymers	Exposure Period	Estimated Intake of Catechin Monomers (mg/person/day)	Measured Outcome	Reference
1 healthy female	Canned green tea	Single dose	~176 mg total catechin[4]	Urinary excretion of catechins	Yang *et al.*, 2000
5 healthy males	Decaffeinated green tea powder	Single dose	~300 mg total catechin[5]	Urinary excretion of EGC, EC, and metabolites ↑ plasma levels of EGC and EC	Li *et al.*, 2000
1 healthy male	Decaffeinated green tea powder	Single dose	~300 or 600 total catechins[6]	Urinary excretion of EGC, EC, and metabolites ↑ plasma levels of EGC and EC	Li *et al.*, 2000
2 healthy females 1 healthy male	Green tea leaf extract (capsules)	Single dose	233, 388, or 543 mg EGCG and EGC combined	↑ plasma levels of EGCG and EGC	Nakagawa *et al.*, 1997
20 healthy males and females	Epigallocatechin gallate capsules	Single dose	200, 400, 600, or 800 mg EGCG	EGCG and EGC and EC conjugates in plasma and urine	Chow *et al.*, 2001
20 healthy males and females	Polyphenon E capsule	Single dose	268, 536, 804, or 1,072 mg total catechins	EGCG and EGC and EC conjugates in plasma and urine	Chow *et al.*, 2001
15 healthy females	Black tea powder	6 hours (4 doses/day)	100 mg total catechins	↑ plasma levels of EGC, EGCG, EC, and ECG ↑ urinary levels of EGC and EC ↑ fecal levels of EGC, EGCG, EC, and ECG	Warden *et al.*, 2001
5 healthy males 4 healthy females	Red wine	Single dose	35 mg (+)-catechin	↑ plasma levels of (+)-catechin metabolites	Donovan *et al.*, 1999

Table 3 Grape Seed Extract and Monomeric Constituent Intakes of Subjects in Prospective Clinical Trials and Epidemiological Studies					
Number of Subjects	**Source of Monomers and/or Polymers**	**Exposure Period**	**Estimated Intake of Catechin Monomers (mg/person/day)**	**Measured Outcome**	**Reference**
5 healthy males	Chocolate or cocoa	Single dose	~2,740 total polyphenols	↑ EC conjugates in plasma and urine	Baba *et al.*, 2000
4 healthy males	Decaffeinated green tea powder	Single dose	235 mg total catechin[7]	↑ plasma levels of EGCG, EGC, and EC urinary excretion of EGC and EC	Lee *et al.*, 1995
Antioxidant Potential					
9 healthy males	Whisky or red wine	Single dose	180 or 1,251 GAE; µg/mL	↑ total plasma phenolic concentration ↑ plasma antioxidant capacity	Duthie *et al.*, 1998
6 healthy females 4 healthy males	Red wine White wine	Single dose	NR[8]	↑ serum antioxidant capacity	Whitehead *et al.*, 1995
8 healthy females	Strawberry, ascorbic acid, raw spinach, dealcoholized red wine	1day[9]	NR	↑ serum antioxidant capacity	Cao *et al.*, 1998
18 healthy subjects	Green or black tea[10]	3 days	400 or 1,040 total catechins	↑ plasma concentration of total catechins No effect on serum antioxidant capacity	van het Hof *et al.*, 1999
17 healthy males	Red wine	2 weeks	800 mL red wine/day	↓ plasma and LDL lipid peroxidation	Fuhrman *et al.*, 1995

Table 3 Grape Seed Extract and Monomeric Constituent Intakes of Subjects in Prospective Clinical Trials and Epidemiological Studies

Number of Subjects	Source of Monomers and/or Polymers	Exposure Period	Estimated Intake of Catechin Monomers (mg/person/day)	Measured Outcome	Reference
Cardiovascular Health Effects					
5 healthy females 5 healthy males	Red and white wine and grape juice	Single dose	300 mL white or red wine or 720 mL grape juice	↓ blood platelet aggregation	Folts, 1998
20 healthy males	Red or white wine	2 weeks	400 mL wine	↑ plasma HDL cholesterol and plasma apolipoprotein A-I concentrations	Lavy *et al.*, 1994
24 healthy males	Red or white wine or grape juice	4 weeks	375 mL wine or 500 mL grape juice	No effect on platelet aggregation or thromboxane production	Pace-Asciak *et al.*, 1996
10 hypercholesterolemic subjects	Grape seed extract	2 months	100 mg grape seed extract	↓ autoantibodies to oxidized LDL	Preuss *et al.*, 2000
939 elderly men	Fruit, vegetables and beverages	1 year	25.9 mg total flavonoids	↓ mortality from coronary heart disease	Hertog *et al.*, 1993
2,748 males 2,385 women	Total diet	6 years	3.4 mg total flavonoids	Inverse association of flavonoid consumption with coronary heart disease	Knekt *et al.*, 1996
552 men enrolled in the Zutphen Study	Total diet	10 years	18.3 to 28.6 mg total flavonoids/day	Inverse association of flavonoid consumption with coronary heart disease	Keli *et al.*, 1996
12,763 men enrolled in Seven Countries Study	Total diet	25-year follow-up period	2.6 to 68.2 mg total flavonoids/day	Inverse association of flavonoid consumption with coronary heart disease	Hertog *et al.*, 1995

Table 3 Grape Seed Extract and Monomeric Constituent Intakes of Subjects in Prospective Clinical Trials and Epidemiological Studies					
Number of Subjects	**Source of Monomers and/or Polymers**	**Exposure Period**	**Estimated Intake of Catechin Monomers (mg/person/day)**	**Measured Outcome**	**Reference**
Chemoprotective Studies					
1,016 esophageal cancer patients 1.552 control subjects	Green tea	Average daily intake	Not reported	Inverse association of green tea consumption with esophageal cancer	Gao *et al.*, 1994
12,763 men enrolled in Seven Countries Study	Total diet	Average daily intake with 25-year follow-up period	2.6 to 68.2 mg total flavonoids/day	No association with cancer mortality	Hertog *et al.*, 1995

Abbreviations: EGC = (-)-epigallocatechin; EGCG = (-)-epigallocatechin gallate; ECG = (-)-epicatechin gallate; EC = (-)-epicatechin; GAE = gallic acid equivalents

[1] Randomized cross-over sequence; each person received each dose, separated by 1-week washout periods

[2] Each subject consumed 5g green tea powder (2.1% (-)-epigallocatechin by dry weight) in water

[3] Each g of decaffeinated green tea extract contained 73 mg EGCG, 68 mg EGC, 22 mg ECG, and 25 mg EC

[4] Subject consumed 340 mL green tea, which contained 51.86 mg catechins/100 mL

[5] Each subject consumed 1.2g green tea powder, either once or twice a day, which consisted of approximately 25% catechins (dry weight basis)

[6] Each subject consumed 1.2g green tea powder 2x per day (once every 12 hours) which consisted of approximately 25% catechins (dry weight basis)

[7] Dose of green tea powder contained 88 mg EGCG, 82 mg EGC, 33 mg ECG, and 32 mg EC

[8] Not reported

[9] Each subject consumed each treatment for 1 day, separated by a 1-week washout period

[10] 1 cup of tea or water every 2 hours (8 cups/day)

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Attachment I

ATTACHMENT 1

CURRICULA VITAE OF EXPERT PANEL MEMBERS

Joseph Francis Borzelleca

Educational Background:

B.S. St. Joseph's University, Philadelphia, PA, Major: Biology, Chemistry.

M.S. School of Graduate Studies, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA, Major: Pharmacology, Physiology.

Ph.D. School of Graduate Studies, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA. Major: Pharmacology, Biochemistry.

Academic Appointments

Instructor-Associate: Department of Pharmacology, Medical College of Pennsylvania, 1956-1959.

Assistant Professor: Department of Pharmacology, Toxicology, Medical College of Virginia, 1959-62 and 1962-1967.

Professor: Department of Pharmacology, Toxicology, Medical College of Virginia, 1967-

Head: Division of Toxicology, Department of Pharmacology, Toxicology, Medical College of Virginia, 1972-1986.

Professor Emeritus: Pharmacology & Toxicology, Department of Pharmacology, Toxicology, Medical College of Virginia, July 1996 –

Professional Certification

Fellow, Academy of Toxicological Sciences

Professional Affiliations

Societies

Academy of Toxicological Sciences* **

American Association for the Advancement of Science

American Chemical Society

American College of Toxicology*

American Society of Pharmacology and Experimental Therapeutics**

(Environmental Pharmacology Committee; Liaison Committee, SOT; Toxicology Committee)

International Society of Regulatory Toxicology and Pharmacology*

(Member of Council)

Sigma XI

Society of Experimental Biology and Medicine*

(Councilor; Program Chairman of Southeastern Section)

Society for Risk Analysis

Society of Toxicology* **
(Member and/or Chairman: Awards, Education, Legislative Affairs, Membership, Nominating Committees; Secretary of the Society, Councilor, and President; President, Food Safety Specialty Section)

Virginia Academy of Science*

(Chairman, Medical Sciences Division)

* Held elected office
** Held appointed office or position

Board of Directors

ILSI

Board of Scientific and Policy Advisors

American Council on Science and Health

Journals

Editor, Food Chemical Toxicology, 1992-

Editorial Board

Environmental Carcinogenesis Reviews, 1981-

Journal of Environmental Pathology, Toxicology and Oncology 1977-

Journal of Environmental Science and Health, 1979-

Journal of the American College of Toxicology, 1982-

Journal of Toxicology: Cutaneous and Ocular Toxicology, 1982- 1992

Journal of Applied Toxicology, 1989-

Pharmacology, 1978-

Pharmacology and Drug Development, 1980-

Toxicology and Applied Pharmacology, 1975-1978

Consultantships (Past, Present)

Governmental

- Food and Drug Administration
- National Institute of Mental Health
- National Cancer Institute
- Environmental Protection Agency
- Department of Labor - OSHA (Chairman, Carcinogens Standards Committee)
- U.S. Army - Research and Development Command

Non-Governmental

- National Academy of Sciences - NRC
  - Committee on Toxicology (Member, Chairman)/Board on Toxicology and Environmental Health Hazards
  - Safe Drinking Water Committee
  - Evaluation of Household Substances Committee (1138 Committee)
  - Food Protection Committee
  - Food Additives Survey Committee
  - Committee on Risk-Based Criteria for Non-RCRA Hazardous Wastes
  - Committee on Risk Assessment of Flame-Retardant Chemicals
- Federation of American Societies of Experimental Biology
  - Select Committee on GRAS Substances
  - Flavors and Extracts
  - Biotechnology Product Safety
  - Caprenin GRAS Committee
- World Health Organization
  - Joint Meeting on Pesticide Residues (JMPR) (Member, Chairman)
- NATO/CCMS Drinking Water Committee

Industrial

- Chemical Companies; Trade Associations

University Activities

Related to Instruction

Prepared a laboratory manual in pharmacology (animal and human studies) (1960)
Introduced the use of closed circuit TV and TV tapes in pharmacology (11960)
Introduced clinical pharmacological experiments into the medical and dental programs (1960)

Planning and participation in continuing education program
(Schools of Dentistry, Medicine and Pharmacy)

Planning and administering each of the three major efforts in pharmacology

(dental, medical, pharmacy) since 1960.

Graduate Program - assisted in developing graduate training program in toxicology

Current Teaching Activities

Presents lectures on Toxicological Issues, Food Intake and Control

Not Directly Related to Instruction

Elected senator from the graduate school, then vice-president of the University Senate
Served on various committees (e.g. Curriculum, Search, Animal Care) in each of the four major schools (Dentistry, Graduate, Medical, Pharmacy)

Research

Research was continuously funded from 1956. Sources of support included governmental (U.S.P.H.S.; N.I.H; E.P.A.; N.I.D.A.) and non-governmental (industrial). A list of publications is attached).

Awards

DOD - US Army - Chemical Research Development and Engineering Center

Distinguished Service Award, 1986

National Italian - American Foundation Award

Excellence in Medicine and Community Service, 1987

Thomas Jefferson University

Distinguished Alumnus Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences

Outstanding Faculty Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences, Dept. of Pharmacology and Toxicology

Professor of the Year- 1992

American College of Toxicology

Distinguished Service Award- 1997

Virginia's Life Achievement in Science Award- April 2001

2001 Bernard L. Oser Food Ingredient Safety Award by the Institute of Food Technologists

PUBLICATIONS

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Borzelleca, J.F.: "History of Toxicology." In Principles and Methods of Toxicology (Hayes, A.W., editor), edition 3, Chap. 1, p 1-18, Raven Press, New York, NY. 1994

Matt, D.W. and Borzelleca, J.F.: "Toxic Effects on the Female Reproductive System During Pregnancy, Parturition, and Lactation." In Reproductive Toxicology (Witorsch, R.J., editor), edition 2, chapter 10, p. 175 Raven Press, New York, NY. 1995

Borzelleca, J.F.: "Food-Borne Health Risks: Food Additives, Pesticides and Microbes." In Nutrition Policy in Public Health (Bronner, F., editor). Chap. 3, p.33, Springer Publishing Co. New York, NY. 1997

Rice, R.G., Graham, D.M., Glaze, W.H., Pariza, M.W., Newell, G.W., Erdman, J.W., and Borzelleca, J.F.: Ozone Preservation of Foods and Foodstuffs. 13th Ozone World Congress, Kyoto, Japan, October 1997

Borzelleca, J.F. and Weiner, M.L. : "Development of Safety Evaluation Guidelines." In Excipient Toxicity and Safety (Weiner, M. L. and Kotkoskie, L. A., editors). Chapter 5, p.101. Marcel Dekker, Inc., New York, N.Y. 1999

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Research Office, Federation of American Societies of Experimental Biology (FASEB):

Evaluation of the health aspects of iron and iron salts as food ingredients. 1973.

Evaluation of the health aspects of butylated hydroxytoluene as a food ingredient. 1973.

Evaluation of the health aspects of certain zinc salts as food ingredients. 1973.

Evaluation of the health aspect of pulps as they may migrate to food from packaging materials. 1973.

Evaluation of the health aspects of propylene glycol and propylene glycol monostearate as food ingredients. 1973.

Evaluation of the health aspects of alginates as food ingredients. 1973.

Evaluation of the health aspects of agar-agar as a food ingredient. 1973.

Evaluation of the health aspects of certain red and brown algae as food ingredients. 1973.

Evaluation of the health aspects of cellulose and certain cellulose derivatives of food ingredients. 1973.

Iodine in foods: chemical methodology and sources of iodine in the human diet. 1974.

Evaluation of the health aspects of aconitic acid as a food ingredient. 1974.

Evaluation of the health aspects of stannous chloride as a food ingredient. 1974.

Evaluation of the health aspects of licorice, glycyrrhiza and ammoniated glycrrhizin as food ingredients. 1974.

Evaluation of the health aspects of Gaprylic acid as a food ingredient. 1974.

Evaluation of the health aspects of sorbose as a food ingredient. 1974.

Evaluation of the health aspects of sulfuric acid and sulfates as food ingredients. 1974.

Evaluation of the health aspects of potassium iodide, potassium iodate, and calcium iodate as food ingredients. 1975.

Evaluation of the health aspects of dextran as food ingredients. 1975.

Evaluation of the health aspects of calcium oxide and calcium hydroxide as food ingredients. 1975.

Evaluation of the health aspects of succinic acid as a food ingredient. 1975.

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of certain calcium salts as food ingredients. 1975.

Evaluation of the health aspects of glycerin and glycerides as food ingredients 1975

Evaluation of the health aspects of dextrin and corn dextrin as food ingredients. 1975.

Evaluation of the health aspects of sodium thiosulfate as a food ingredient. 1975.

Evaluation of the health aspects of gelatin as a food ingredient. 1975.

Evaluation of the health aspects of bile salts and ox bile extract as food ingredients. 1975.

Evaluation of the health aspects of choline chloride and choline bitartrate as food ingredients. 1975.

Evaluation of the health aspects of aluminum compounds as food ingredients. 1975.

Evaluation of the health aspects of tallow, hydrogenated tallow, stearic acid, and calcium stearate as food ingredients. 1975.

Evaluation of the health aspects of phosphates as food ingredients. 1975.

Evaluation of the health aspects of the tocopherols and a-tocopheryl acetate as food ingredients. 1975.

Evaluation of the health aspects of sorbic acid and its salts as food ingredients. 1975.

Evaluation of the health aspects of hydrogenated fish oil as a food ingredient. 1975.

Evaluation of the health aspects of beeswax (yellow or white) as a food ingredient. 1975.

Evaluation of the health aspects of inositol as a food ingredient. 1975.

Evaluation of the health aspects of malic acid as a food ingredient. 1975.

Evaluation of the health aspects of Japan Wax as a substance migrating to food from cotton or cotton fabrics used in dry food packaging. 1976.

Evaluation of the health aspects of carnauba wax as a food ingredient. 1976.

Evaluation of the health aspects of sulfamic acid as it may migrate to foods from packaging materials. 1976

Evaluation of the health aspects of hydrosulfites as they may migrate to foods from packaging materials. 1976.

Evaluation of the health aspects of gum guaiac as a food ingredient. 1976.

Contributing authorship on the following publications of the Life Science Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of tall oil as it may migrate to foods from packaging materials. 1976

Evaluation of the health aspects of corn sugar (dextrose), corn syrup and invert sugar as food ingredients. 1976.

Evaluation of the health aspects of sucrose as a food ingredient. 1976.

Evaluation of the health aspects of sulfiting agents as food ingredients. 1976.

Evaluation of the health aspects of glycerophosphates as food ingredients. 1976.

Evaluation of the health aspects of magnesium salts as food ingredients. 1976. Evaluation of the health aspects of sodium hydroxide and potassium hydroxide as food ingredients. 1976.

Evaluation of the health aspects of adipic acid as a food ingredient. 1976.

Evaluation of the health aspects of hydrogenated soybean oil as a food ingredient.

Evaluation of the health aspects of formic acid, sodium formate, and ethyl formate as food ingredients. 1976.

Evaluation of the health aspects of lard and lard oil as they may migrate to foods from packaging materials. 1976.

Evaluation of the health aspects of pyridoxine and pyridoxine hydrochloride as food ingredients. 1977.

Evaluation of the health aspects of papain as a food ingredient. 1977.

Evaluation of the health aspects of hypophosphites as food ingredients. 1977.

Evaluation of the health aspects of coconut oil, peanut oil, and oleic acid as they migrate to food from packaging materials, and linoleic acid as a food ingredient. 1977.

Evaluation of the health aspects of pectin and pectinates as food ingredients. 1977.

Evaluation of the health aspects of tannic acid as a food ingredient. 1977.

Evaluation of the health aspects of rennet as a food ingredient. 1977.

Evaluation of the health aspects of acetic acid and sodium acetate as food ingredients. 1977.

Evaluation of the health aspects of sodium oleate and sodium palmitate as substances migrating to food from paper and paperboard used in food packaging. 1977.

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of corn silk as a food ingredient. 1977.

Evaluation of the health aspects of bentonite and clay (kaolin) as food ingredients. 1977

Evaluation of the health aspects of citric acid, sodium citrate, potassium citrate, calcium citrate, ammonium citrate, triethyl citrate, isopropyl citrate, and stearyl citrate as food ingredients. 1977.

Evaluation of the health aspects of lactic acid and calcium lactate as food ingredients. 1978.

Evaluation of the health aspects of calcium pantothenate, sodium pantothenate, and D-pantothenyl acohol as food ingredients. 1978.

Evaluation of the health aspects of Vitamin B12 as a food ingredient. 1978.

Evaluation of the health aspects of Vitamin D2 and Vitamin D3 as food ingredients. 1978.

Evaluation of the health aspects of caffeine as a food ingredient. 1978.

Evaluation of the health aspects of certain glutamates as food ingredients. 1978.

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1978.

Evaluation of the health aspects of butylated hydroxyanisole as a food ingredient. 1978.

Evaluation of the health aspects of sodium, potassium, magnesium and zinc gluconates as food ingredients. 1978.

Evaluation of the health aspects of urea as a food ingredient. 1978.

Evaluation of the health aspects of thiamin hydrochloride and thiamin mononitrate as food ingredients. 1978.

Evaluation of the health aspects of biotin as a food ingredient. 1978.

Evaluation of the health aspects of ascorbic acid, sodium ascorbate, calcium ascorbate, erythorbic acid, sodium erythorbate, and ascorbyl palmitate as food ingredients. 1979.

Evaluation of the health aspects of propionic acid, calcium propionate, sodium propionate, dilauryl thiodipropionate, and thiodipropionic acid as food ingredients. 1979.

Evaluation of the health aspects of casein, sodium Gaseinate, and calcium caseinate as food ingredients. 1979.

Evaluation of the health aspects of nickel as a food ingredient. 1979

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of soy protein isolates as food ingredients. 1979.

Evaluation of the health aspects of carotene (B-carotene) as a food ingredient. 1979.

Evaluation of the health aspects of nitrogen, helium, propane, n-butane, isobutane, and nitrous oxide as gases used in foods. 1979.

Evaluation of the health aspects of hydrogen peroxide as a food ingredient. 1979.

Evaluation of the health aspects of riboflavin and riboflavin-5-1-phosphate as food ingredients. 1979.

Evaluation of the health aspects of starch and modified starches as food ingredients. 1979.

Evaluation of the health aspects of carbon dioxide as a food ingredient. 1979.

Evaluation of the health aspects of sodium chloride and potassium chloride as food ingredients. 1979.

Evaluation of the health aspects of certain silicates as food ingredients. 1979.

Evaluation of the health aspects of manganous salts as food ingredients. 1979.

Evaluation of the health aspects of copper gluconate, copper sulfate, and cuprous iodide as food ingredients. 1979.

Evaluation of the health aspects of hydrochloric acid as a food ingredient. 1979.

Evaluation of the health aspects of lecithin as a food ingredient. 1979.

Evaluation of the health aspects of potassium acid tartrate, sodium potassium tartrate, sodium tartrate and tartaric acid as food ingredients. 1979.

Evaluation of the health aspects of starter distillate and diacetyl as food ingredients. 1980.

Vitamin A, Vitamin A Acetate, and Vitamin A Palmitate as food ingredients. 1980.

Evaluation of the health aspects of iron and iron salts as food ingredients. 1980.

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1980.

Evaluation of the health aspects of collagen as a food ingredient. 1981.

Evaluation of the health aspects of methyl polysilicones as food ingredients. 1981

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PROFESSIONAL EXPERIENCE

2000 to present, University of California, Davis, Professor of Enology

1999 to present, Vice Chair

1998 to 2000, Chair of Agricultural and Environmental Chemistry Graduate Group

1997-2000, Associate Professor of Enology, Agricultural and Environmental Sciences, Viticulture and Enology University of California, Davis

1991-1997, Assistant Professor, University of California, Davis, Agricultural and Environmental Sciences, Viticulture and Enology

1986 to 1991, Tulane University, Assistant Professor of Chemistry

1985-1986, University of California, Berkeley, Pesticide Chemistry and Toxicology Laboratory, Research Specialist

1983-1985, University of California, Berkeley, Postdoctoral Chemistry Researcher

1977-1983, University of California, Berkeley, Chemistry Department, Research Assistant/Teaching Assistant

EDUCATION

University of California, Berkeley
Ph.D. in Organic Chemistry, 1983
University of Notre Dame
B.S. in Chemistry, with honors, 1977

AFFILIATIONS

American Society for Enology and Viticulture Board Member (1996-2000)
Sigma Xi
American Chemical Society
Group Polyphenols
Phytochemical Society of North America

AWARDS

2000 Chancellor's Fellow, University of California, Davis
1996 Wine Research Award, Society of Medical Friends of Wine
1995 Award of Special Merit, Academie Amorim

PEER REVIEW

Associate Editor: American Journal of Enology and Viticulture, Journal of the Science of Food and Agriculture, Advisory Board: Journal of Agricultural and Food Chemistry, reviewer for American Journal of Clinical Nutrition, Italian Journal of Food Science, Journal of Nutrition, Free Radical Biology & Medicine, Journal of Food Biochemistry

SYMPOSIA

Wine in Context: Wine and Health, American Society for Enology and Viticulture, Reno, 1996

Chemistry of Wine Flavor, American Chemical Society, San Francisco, 1997

Oak in Winemaking, American Society for Enology and Viticulture, Reno, 1999 (Proceedings published in AJEV:50 (4), 1999)

PUBLICATIONS

Zimman A, Joslyn WS, Lyon ML, Meier J, Waterhouse AL. Maceration Variables Affecting Phenolic Composition in Commercial-Scale Cabernet Sauvignon Winemaking Trials. American Journal of Enology and Viticulture 53; in press.

Ibern-Gomez M, Andres-Lacueva C, Lamuela-Raventos RM, Waterhouse AL. Rapid HPLC Method for Phenolic Compounds in Red Wines. American Journal of Enology and Viticulture 53; in press.

Kennedy JA, Matthews MA, Waterhouse AL. Effect of Maturity and Vine Water Status on Grape Skin and Wine Flavonoids. American Journal of Enology and Viticulture. 53; in press.

Bisson LF, Waterhouse AL, Ebeler SE, Walker MA, Lapsley JT. The present and future of the international wine industry. Nature 418(6898):696-9, 2002

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Donovan JL, Luthria DL, Stremple P, Waterhouse AL. Analysis of (+)-catechin, (-)-epicatechin and their 3'- and 4'-O-methylated analogs. A comparison of sensitive methods. J Chromatogr B Biomed Sci Appl 726(1-2):277-83, 1999.

Donovan JL, McCauley JC, Tobella Nieto N, Waterhouse AL. Effects of small-scale fining on the phenolic composition and antioxidant activity of Merlot wine. in Chemistry of Wine Flavor, Waterhouse, A.L. and S.E. Ebeler, eds. American Chemical Society, Washington, DC, pp. 142-155, 1999.

Ritchey JG, Waterhouse AL. A standard red wine: monomeric phenolic analysis of commercial Cabernet Sauvignon wines. American Journal of Enology and Viticulture 50:91-100, 1999.

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Waterhouse AL, Price SF, McCord JD. Reversed-Phase High-Performance Liquid Chromatography Methods for Analysis of Wine Polyphenols, Methods in Enzymology 299: 113-121, 1999.

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Matricardi L, Waterhouse AL. Influence of toasting technique on color and ellagitannins of oak wood in barrel making. American Journal of Enology and Viticulture. 50: 519-526, 1999.

Bell JR; Donovan JL; Wong R; Waterhouse AL; German JB; Walzem RL; Kasim-Karakas SE. Catechin in human plasma after ingestion of a single serving of reconstituted red wine. Am J Clin Nutr. 71(1): 103-8, 2000.

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Waterhouse A L;German J B;Walzem R L;Hansen R J;Kasim-Karakas S E. Is it time for a wine trial?. American Journal of Clinical Nutrition. 68(2): 220-1, 1998.

Lamuela-Raventos, R.M., A.L. Waterhouse. Resveratrol and Piceid in Wine. Methods in Enzymology. 299: 184-190, 1998.

Clifford A J;Ebeler S E;Ebeler J D;Bills N D;Hinrichs S H;Teissedre P L;Waterhouse A L. Delayed tumor onset in transgenic mice fed an amino acid-based diet supplemented with red wine solids.. American Journal of Clinical Nutrition. 64(5): 748-56, 1996.

Waterhouse AL, Shirley JR, Donovan JL. Antioxidants in chocolate. Lancet. 348(9030): 834, 1996.

Towey, J.P; Waterhouse, A.L., The extraction of volatile compounds from French and American oak barrels in Chardonnay during three successive vintages, Am. J. Enol. Vitic 47, 1996.

Romero-Perez, A.I; Lamuela-Raventos, R.M; Waterhouse, A.L; de la Torre-Boronat, M.C., Levels of cis- and trans-resveratrol and their glycosides in white and rose Vitis vinifera wines from Spain, J. Agric. Food Chem., 44: 2124-2128, 1996.

Liu J;Waterhouse A L;Chatterton N J. Proton and carbon NMR chemical-shift assignments for [beta-D-Fru f-(2-->1)]3-(2<==>1)-alpha-D-Glc p (nystose) and [beta-D-Fru f-(2-->1)]4-(2<==>1)-alpha-D-Glc p (1,1,1-kestopentaose) from two-dimensional NMR spectral measurements.. Carbohydrate Research. 245(1): 11-9, 1993.

Frankel E N;Waterhouse A L;Kinsella J E. Inhibition of human LDL oxidation by resveratrol. Lancet. 341(8852): 1103-4, 1993.

Waterhouse A L;Horvath K;Liu J. Conformational analysis of beta-D-fructofuranosyl-(2-->6)-beta-D-glucopyranoside by molecular mechanics (MM2) calculations.. Carbohydrate Research. 235: 1-13, 1992.

Liu J;Waterhouse A L. Conformational analysis of levanbiose by molecular mechanics.. Carbohydrate Research. 232(1): 1-15, 1992.

Liu J H;Waterhouse A L;Chatterton N J. Proton and carbon chemical-shift assignments for 6-kestose and neokestose from two-dimensional n.m.r. measurements.. Carbohydrate Research. 217: 43-9, 1991.

Waterhouse A L;Calub T M;French A D. Conformational analysis of 1-kestose by molecular mechanics and by n.m.r. spectroscopy.. Carbohydrate Research. 217: 29-42, 1991.

Calub T M;Waterhouse A L;French A D. Conformational analysis of inulobiose by molecular mechanics.. Carbohydrate Research. 207(2): 221-35, 1990.

CURRICULUM VITAE
GARY MURRAY WILLIAMS, M.D.

EDUCATION: Washington and Jefferson College,
Washington, Pa. B.A. 1963; Magna Cum Laude

University of Pittsburgh School of Medicine,
Pittsburgh, Pa. M.D., 1967

SUBSEQUENT TRAINING AND POSITIONS;

1967-1969	Intern and Resident in Pathology, Department of Pathology, Massachusetts General Hospital and Instructor in Pathology, Harvard University Medical School, Boston, Massachusetts.
1969-1971	Staff Associate, National Cancer Institute, Experimental Pathology Branch, Chemical Carcinogen Screening Unit, Bethesda, Maryland.
1971-1972	Visiting Scientist, Wenner-Gren Institute, Department of Cell Physiology, Stockholm, Sweden.
1971-1975	Assistant Professor, Department of Pathology, and Member, Fels Research Institute, Temple University School of Medicine, Philadelphia, Pennsylvania.
1975-1979	Chief, Division of Experimental Pathology, American Health Foundation; and Research Associate Professor, Department of Pathology, New York Medical College, Valhalla, New York.
1979-1980	Chief, Division of Pathology and Toxicology, American Health Foundation; and Research Professor, Department of Pathology, New York Medical College, Valhalla, New York.

1980-1987	Associate Director and Chief, Division of Pathology and Toxicology, American Health Foundation; Research Professor, Department of Pathology, New York Medical College, Valhalla, New York.
1987-1997	Director of Medical Sciences and Chief, Division of Pathology and Toxicology, American Health Foundation; Research Professor, Department of Pathology, New York Medical College, Valhalla, New York.
1997-1998	Director, Naylor Dana Institute and Chief, Division of Pathology and Toxicology, American Health Foundation; Research Professor, Department of Pathology, New York Medical College, Valhalla, New York; Visiting Lecturer, Graduate School of Health Sciences, New York Medical College, Valhalla, New York.
1999 - present	Professor of Pathology, Department of Pathology, Director of Environmental Pathology and Toxicology, Head, Program on Medicine, Food and Chemical Safety, New York Medical College, Valhalla, New York; Affiliated Faculty, Graduate School of Health Sciences, New York Medical College, Valhalla, New York.

CERTIFICATIONS:

1974	American Board of Pathology
1975	Physician, State Education Department, State of New York
1981	American Board of Toxicology, Recertified, 2002.
1984	Expert in Toxicology, Ministere des Affaires Sociales et de la Solidarite Nationale, Direction de la pharmacie et du medicament, Republic Francais
2000	Fellow in Toxicologic Pathology, International Academy of Toxicologic Pathology

AWARDS AND HONORS:

1963	Phi Beta Kappa, Washington and Jefferson College
1967	Sheard-Sandford Award, American Society of Clinical Pathologists

1967	Alpha Omega Alpha, University of Pittsburgh School of Medicine
1971	Research Training Fellowship, International Agency for Research on Cancer
1980	Association of University Pathologists
1981	Invited Contributor, Special Issue Food and Cosmetics Toxicology, 9:557, 1981, dedicated to Leon Goldberg
1982	Arnold J. Lehman Award, Society of Toxicology
1984	Invited Contributor Hommage au Professeur Rene Truhaut
1987	Citation Classics: Cancer Lett. 1:231, 1976 and Cancer Res. 37:1845, 1977. Institute for Scientific Information, Current Contents, Vol. 30, No.36, September 7, 1987
1988	Citation Classics: In Vitro 12:521, 1976; 12:821, 1976; 13:809, 1977, 14:824, 1978. Institute for Scientific Information. Current Contents, Vol. 32, No. 9, February 27, 1989
1989	Featured on cover of Cancer Research, Volume 49, November 1
1995	Featured on cover of Cancer Research, Volume 55, April 15
1996	Awards Lecture, Society of Toxicology
1997	Invited Contributor, Special Issue Cancer Letters, 118:1, 1997, dedicated to Phillipe Shubik
1998	Top 10 Most Frequently Cited Articles in 25 years of Toxicologic Pathology Toxicologic Pathology 10:3-10, 1982; Toxicologic Pathology 26:452, 1998
2001	Ambassador in Toxicology Award, Mid-Atlantic Chapter of the Society of Toxicology.
2002	Enhancement of Animal Welfare Award, Society of Toxicology.

RECOGNITION:

1996-01	Who's Who in American/50th-56th Editions

1996-00	Who's Who in the East/26-28th Editions
1996-03	Who's Who in Science and Engineering/3rd-6th Editions
1997/1998	American Men and Women of Science Directory of American Research & Technology
1998-00	Official American Board of Medical Specialties Directory of Board Certified Medical Specialists 30th-33rd Editions

SOCIETIES:

1974	American Association for Cancer Research
1978	Society of Toxicology
1981	Society of Toxicologic Pathologists
1991	International Society of Regulatory Toxicology and Pharmacology

EDITORIAL RESPONSIBILITIES:

1980	Co-Editor, Differentiation and Carcinogenesis in Liver Cell Cultures. Vol. 349. New York Academy of Sciences.
1980-1981	Consulting Reviewer, Oncology Overviews, International Cancer Research Data Bank.
1980-1986	Reviewing Editor, In Vitro.
1980	Co-editor, The Predictive Value of In Vitro Short-term Screening Tests in Carcinogenicity Evaluation. Elsevier/North Holland Biomedical Press.
1981-1983	Editorial Board, Fundamental and Applied Toxicology.
1981-1989	Editorial Board, Toxicology and Applied Pharmacology.
1981-1999	Editorial Board, Nutrition and Cancer.
1981	Meeting Report: Carcinogenesis and Gene Expression in Liver Cultures. Cancer Research 42:2462-2464, 1982.
1982	Consulting Reviewer, Oncology Overview, International Cancer Research

Data Bank Program, National Cancer Institute.

1982-1993 Editorial Board, Mutation Research, Genetic Toxicology Testing Section.

1983 Co-Editor, Colon Carcinogenesis. CRC Press.

1983 Co-Editor, Cellular Systems for Toxicity Testing. Vol. 407. New York Academy of Sciences.

1983 Co-Editor, Tests Courts de Cancerogenese/Short-term Tests for Carcinogenesis, Elsevier Science Publishers BV, Amsterdam.

1983-1992 Editorial Board, Chemico-Biological Interactions.

1983-1996 Editorial Board, Toxicologic Pathology.

1984-present Founding Editor, Cell Biology and Toxicology.

1987 Meeting Report: Causative and Modifying Factors in Digestive Tract Cancer. Cancer Research 47:922-923, 1987

1988-present Editorial Board, Archives of Toxicology

1988 Editor, Sweeteners: Health Effects, Princeton Scientific Publishing Company.

1989 Editorial Board, Complex Mixtures and Cancer Risk, IARC Scientific Publications, International Agency for Research on Cancer

1990 Meeting Report: American Health Foundation 20th Anniversary International Symposium on Causes and Prevention of Cancer. Preventive Medicine, in 20:534-547, 1991

1991-present International Advisory Board, European Journal of Cancer Prevention

1992 Proceedings of the Second International Conference on Longevity and Aging: Environmental and Nutritional Influences on Aging and Cancer Experimental Gerontology, Volume 27, Special Issue, 1992

1993 Editor-in-Chief, Antioxidants Chemical, Physiological, Nutritional and Toxicological Aspects, Princeton Scientific Publish. Co.

1994-present Area Editor for Carcinogenesis, Drug and Chemical Toxicology.

1997 Co-Editor, Reducing Dietary Fat: Putting Theory into Practice, Journal

of The American Dietetic Association, Volume 97, Supplement 1, 1997

2001 Co-Editor, Toxicology, Special Issue, Volume 166, Number 3, Festschrift J.H. Weisburger.

MEETINGS ORGANIZED:

1980 Conference on Differentiation and Carcinogenesis in Liver Cell Cultures. New York Academy of Sciences. New York, NY.

1980 Workshop on the Predictive Value of in vitro Short Term Screening Tests in the Evaluation of Carcinogenicity. Scientific Council of the Netherlands Cancer Society. Dalen, The Netherlands.

1982 Quo Vadis Symposium on Short Term Tests in Carcinogenesis and Mutagenesis. Research Center Clin-Midy. Montpellier, France.

1983 Conference on Carcinogenesis and Gene Expression in Liver Cultures United States-Japan Cooperative Cancer Research Program. Honolulu, Hawaii.

1984 Conference on Cellular Systems for Toxicity Testing, New York Academy of Sciences, New York, NY.

1986 Conference on Causative and Modulating Factors for Digestive Tract Cancer United States-Japan Cooperative Cancer Research Program. Tokyo, Japan.

1986 International Conference on Cancer Research. Theories of Carcinogenesis. The Norwegian Cancer Society, Oslo, Norway.

1986 Conference on Non-Mutagenic Carcinogens: How Much Risk to Man? The Robens Institute, University of Surrey, Guildford, England.

1987 Conference on Sweeteners: Health Effects. American Health Foundation, New York.

1987 International Symposium in Genetic Toxicology, National Science Foundation (U.S.) and Council of Scientific and Industrial Research (India), University of Calcutta, Calcutta, India.

1988 International Symposium on Causes and Prevention of Cancer, American Health Foundation in cooperation with American Cancer Society and National Cancer Institute, New York, NY.

1989 International Conference on Environmental and Nutritional Influences on

Aging and Cancer, American Health Foundation in cooperation with National Institute on Aging, New York, NY.

1990 Conference on Cancer Prevention for Black Americans, Metropolitan Life Insurance, Company, New York, NY.

1991 International Conference on Antioxidants: Chemical, Physiological, Nutritional and Toxicological Aspects, American Health Foundation, Tarrytown, NY.

1991 Second International Conference on Theories of Carcinogenesis. Norwegian Cancer Society, Oslo, Norway.

1992 1st International Short Course on Preclinical Drug and Chemical Safety, Tarrytown, NY.

1993 2nd International Short Course on Preclinical Drug and Chemical Safety, Tarrytown, NY.

1993 American Health Foundation, 25th Anniversary Conference and Celebration, Toward Optimal Health: Examining Goals for Nutrition and the Environment, Tarrytown, NY.

1994 3rd International Course on the Safety Assessment of Pharmaceuticals, Tarrytown, NY.

1995 International Congress on Hepatocytes-Applications in Cell Biology, Toxicology and Medicine, Tubingen, Germany.

1996 Conference, Reducing Dietary Fat: Putting Theory Into Practice, American Health Foundation, New York, NY.

1996 4th International Course on the Safety Assessment of Pharmaceuticals, Part I, White Plains, NY.

1996 4th International Course on the Safety Assessment of Pharmaceuticals, Part II, San Francisco, CA.

1997 5th International Course on the Safety Assessment of Medicines, Part I, White Plains, NY.

1998 6th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.

2000 7th International Course on the Safety Assessment of Medicine.

	Basic and Regulatory Aspects, White Plains, NY.
2001	8th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.
2002	International Symposium on Antimutagenesis and Anticarcinogenesis, New York Medical College, Valhalla, NY

NATIONAL AND INTERNATIONAL RESPONSIBILITIES

1975	Consultant, Pesticides, Toxic Substance and Solid Waste Management, United States Environmental Protection Agency.
1975-1978	Member, Epidemiology Committee, Breast Cancer Task Force, NationalCancer Institute.
1976-1977	Member, Program Committee, American Association for Cancer Research.
1976	Member, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Man: Some Miscellaneous Pharmaceutical Substances, International Agency for Research on Cancer.
1976-1978	Co-Chairperson, Subcommittee on Rat Liver Tumors, Committee on Histologic Classification of Laboratory Animal Tumors, Institute of Laboratory Animal Resources, National Research Council.
1977-1978	Member, Panel on Kepone/Mirex, Scientific and Technical Assessments of Environmental Pollutants, Environmental Studies Board, Commission on Natural Resources, National Research Council.
1979-1980	Member, Panel on Unscheduled DNA Synthesis, Gene-Tox Program, U.S. Environmental Protection Agency.
1980-1981	Member, Panel of Experts Associated with Technical Report Review Subcommittee, National Toxicology Program, Department of Health and Human Services.
1980	Member, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Man-Antineoplastic and Immunosuppressive Drugs, International Agency for Research on Cancer.
1980-1986	Panel of Reviewers, Netherlands Cancer Foundation.
1981	Advisor, Technical Committee, Society of Toxicology.

1981-1982	Member, Task Group on the Differentiation Between Genotoxic and Epigenetic Carcinogens, International Commission on Protection Against Environmental Mutagens and Carcinogens.
1982	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Chemicals and Industrial Processes Associated with Cancer in Humans, IARC Monographs Volumes 1 to 29, International Agency for Research on Cancer.
1982-1983	Consultant, Office of Health and Environmental Assessment, Reproductive Effects Assessment Group, U.S. Environmental Protection Agency.
1982-1983	Member, International Expert Committee to the Nutrition Foundation on the Relevance of Mouse Liver as a Model for Assessing Carcinogenic Risk, Nutrition Foundation, Incorporated.
1982-1983	Coordinator, Assays of DNA Damage, Collaborative Study on Short-Term Tests for Genotoxicity and Carcinogenicity. International Programme on Chemical Safety, World Health Organization.
1983	Member, Working Group on the Mechanisms of Chemical Carcinogenesis, International Agency for Research on Cancer.
1983-1984	Member, Expert Committee on Pathology/Toxicology and Expert Committee on Short-Term Testing, International Life Sciences Institute.
1984-1987	Assessor, National Health and Medical Research Council Panel of Independent Assessors, National Health and Medical Research Council, Commonwealth of Australia.
1984-1985	Member, Committee on the Carcinogenicity of Cyclamates, Food and Nutrition Board, Commission on Life Sciences, National Research Council.
1984-1985	Member, Task Group of DNA Repair, Subcommittee on Genetic Toxicology, American Society for Testing and Materials.
1985-1987	Member, Toxicology Study Section, National Institutes of Health.
1985	Vice-Chairman, Working Group on the Evaluation of the Carcinogenic

	Risk of Chemicals to Humans: Some Naturally Occurring Substances, Food Additives and Amino Acid Pyrolysates in Food, International Agency for Research on Cancer.
1985-1986	Member, Awards Committee, Society of Toxicology.
1986	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42, International Agency for Research on Cancer.
1987	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, International Agency for Research on Cancer.
1988	Participant, Tox-90s Conference, Society of Toxicology.
1989	Organizing Committee, Workshop on the Effects of pesticides on Human Health, Task Force on Environmental Cancer and Heart and Lung Disease.
1989	Chairman, Working Group and Chairman, Subgroup on Animal Carcinogenicity, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Humans: Some Pharmaceutical Drugs, International Agency for Research on Cancer.
1989	Participant and Member of Editorial Board, Workshop on Complex Mixtures and Cancer Risk, International Agency for Research and Cancer.
1989	Participant, Working Group on Short-Term In Vitro and In Vivo Tests, Workshop on Research to Improve Predictions of Long-Term Chemical Toxicity, National Research Council.
1990-present	Member, Committee of Education on Toxicologic Pathology, International Federation of Societies of Toxicologic Pathologists.
1991	Member, Working Group on Approaches to Classifying Carcinogens According to Mechanisms of Action, International Agency for Research on Cancer.

1992-1993	Member, Expert Panel on Interpretive Review of the Potential Adverse Effects of Chlorinated Organic Chemicals on Human Health and the Environment, CanTox, Inc.
1993-1999	Member, Committee on Evaluation of the Research Program "Cancer Risk Factors and Prevention," German Cancer Center.
1993-present	Member, Board of Trustees, International Life Sciences Institute, Health and Environmental Sciences Institute. Chair, Membership Development Committee, 2002.
1993-1999	Member, Cellular Telephone Advisory Committee, Harvard Center for Risk Analysis, Harvard School of Public Health.
1993-1999	Wireless Technology Research Peer Review Board.
1993-present	Member, Subcommittee on Carcinogenicity, International Federation of Societies of Toxicologic Pathologists.
1995-1998	Member, International Committee on Wireless Communication Health Research (ICWCHR).
1995-1997	Member, Committee on Research Opportunities and Priorities for EPA, Commission on Geosciences, Environment, and Resources, National Research Council.
1996	Reviewer, U.S. Environmental Protection Agency (EPA), PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures.
1996	Participant, Developmental Planning for Office of Dietary Supplements (ODS), National Institutes of Health.
1996-1997	Member, Advisory Board to the Calcium Channel Blockers/Cancer Study, Boston University School of Medicine, Slone Epidemiology Unit.
1997	Member, Working Group on Short/Medium Term Carcinogenicity Tests and Genetic and Related Effects. International Agency for Research on Cancer.
1998	Member, Working Group - Re-evaluation of Some Industrial Chemicals. International Agency for Research on Cancer.
1999-present	Member, Subcommittee on Upper Limits, Committee on Reference Levels of Nutrients, National Academy of Sciences, Institute of Medicine.

1999	Member, Working Group on Predictive Value of Gastric Neuroendocrine Tumours and Forestomach Tumours in Rodents for Carcinogenic Hazard Identification. Co-Chairperson, Forestomach Tumors. International Agency for Research on Cancer.
2000	Member and Report Coordinator, Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel. U.S. Environmental Protection Agency.
2001	Reviewer, Office of Dietary Supplements, National Institutes of Health. Annual Bibliography of Significant Advances in Dietary Supplement Research - 2000.
2001-present	Member, Accreditation Committee, International Academy of Toxicologic Pathology.
2002	Peer Review Member, U.S. Environmental Protection Agency "Perchlorate Environmental Contamination: Toxicological Review and Risk Assessment."
2002	WHO Temporary Adviser, 59th Meeting of the Joint Expert Committee on Food Additives (JECFA).

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APPENDIX II

EXPERT PANEL REPORT CONCERNING THE INCREASED USE LEVELS OF GRAPE SEED EXTRACT WITH LESS THAN 5.5% CATECHIN MONOMERS (IH636) IN FOODS

EXPERT PANEL REPORT CONCERNING THE INCREASED USE LEVELS OF GRAPE SEED EXTRACT WITH LESS THAN 5.5% CATECHIN MONOMERS (IH636) IN FOODS

May 15, 2002

Introduction

As independent experts qualified by relevant national and international experience and scientific training to evaluate the safety of food ingredients, we, the undersigned, Joseph F. Borzelleca, Ph.D. (Medical College of Virginia), Andrew L. Waterhouse, Ph.D. (University of California), and Gary Williams, M.D. (New York Medical College), were requested by the manufacturer, Dry Creek Nutrition, Inc., as an Expert Panel (hereinafter referred to as the Panel) to evaluate the impact of increased use levels on the Generally Recognized As Safe (GRAS) status of Grape Seed Extract with less than 5.5% Catechin Monomers (IH636) under the conditions of intended use in conventional foods as an antioxidant and/or emulsifier.

Previously, the safety of IH636 for the same uses (lower use levels) was critically evaluated by the Expert Panel (See attachment 1). The Panel then concluded that the use of IH636 as an antioxidant and/or emulsifier, in a number of foods was GRAS based on scientific procedures. The mean and 90th percentile intake of IH636 by the total population from all proposed food-uses was estimated to be 138 mg/person/day (2.58 mg/kg body weight/day) and 264 mg/person/day (5.46 mg/kg body weight/day), respectively.

In the course of reviewing the impact of increased use levels of IH636, the Expert Panel reviewed intake estimates for the previous GRAS uses and the small increased exposures from higher use levels, information present in the original GRAS dossier, and any additional relevant information.

Following independent, critical evaluation of such data and information, the Expert Panel concluded that under the conditions of increased use levels in foods, IH636 meeting appropriate food grade specifications and manufactured in accordance with current good manufacturing practices, is "generally recognized as safe" based on scientific procedures. A summary of the basis for the Panel's conclusion is provided below.

Dietary Exposure

The proposed uses and use levels of IH636 are shown in the attached Table 1. The food categories of use have not changed from the previous GRAS categories, but there has been some increased use levels in several categories as a result of new technological information. For example, the proposed use levels of IH636 in instant and regular hot cereals, ready to eat cereals, health bars and meal replacements have increased from 0.04% to 0.08%.

The consumption of IH636 from all previous uses and use levels was estimated using the United States Department of Agriculture (USDA) 1994-1996 Continuing Survey of Food Intakes by

Individuals (USDA CSFII 1994-1996) and the 1998 Supplemental Children's Survey (USDA CSF II 1998) (USDA, 2000). The mean and 90th percentile intake of IH636 by the total population from all proposed food-uses was estimated to be 138 mg/person/day (2.58 mg/kg body weight/day) and 264 mg/person/day (5.46 mg/kg body weight/day), respectively. The increase in use levels results in a small increase in exposure. The mean and 90th percentile intake of IH636 by the total population that result from increasing the use levels was estimated to be 153 mg/person/day (2.90 mg/kg body weight/day) and 291 mg/person/day (6.09 mg/kg body weight/day), respectively. IH636 is not intended for use in foods consumed by infants.

Safety Information

The safety of IH636 is based on (a) a history of proanthocyanidin consumption as a result of their abundant natural presence in food, (b) the small quantities expected to be consumed from proposed uses, (c) toxicological and clinical studies on IH636, and (d) metabolic, mutagenicity, toxicological, clinical, and nutritional studies on components of IH636.

In a 90-day oral toxicity study, IH636 was provided to 4 groups Sprague-Dawley rats (20 rats/sex/group) at levels of 0, 0.5, 1.0, or 2.0% (Wren *et al.*, 2001). On a body weight basis, these doses were reported to be equivalent to 0, 348, 642, and 1,586 mg/kg body weight, respectively, for male rats, and 0, 469, 883, and 1,928 mg/kg body weight, respectively, for female rats. The authors reported no compound-related effects on body or organ weights, ophthalmology evaluation, or clinical chemistry or histopathological parameters in any of the animals. No adverse effects were observed up to 2.0% in the diet, the highest dose tested.

Based on toxicological and clinical studies on IH636 reviewed previously and the lack of any recent new information that raises any safety concerns, the increased use levels resulting in increased consumption levels does not impact on the safety of IH636.

Conclusion

We, the Expert Panel, have independently critically evaluated the data and information summarized above and conclude that Grape Seed Extract with less than 5.5% Catechin Monomers, meeting food grade specifications and produced in compliance with cGMP, is Generally Recognized As Safe (GRAS) by scientific procedures for use as an antioxidant and/or emulsifier in conventional foods under the conditions of intended use described herein.

26 May 2002
Date

Joseph Borzelleca, Ph.D.
Professor, Pharmacology and Toxicology
Medical College of Virginia
Virginia Commonwealth University

June 7, 2002
Date

Andrew Waterhouse, Ph.D.
Professor of Enology
Department of Viticulture and Enology
University of California

30 May 2002
Date

Gary Williams, M.D.
Professor of Pathology
Department of Pathology
New York Medical College

000100

Table 1 Summary of the Individual Proposed Food Uses and Use-Levels for Grape Seed Extract with less than 5.5% Catechin Monomers in the U.S.			
Food Category	**Proposed Food Use**	**Use-Levels for Grape Seed Extract with less than 5.5% Catechin Monomers (%)**	
		Previous	**New Proposed**
Beverages and Beverage Bases	Carbonated soft drinks	0.02	0.02
Breakfast Cereals	Instant and regular hot cereals	0.04	0.08
	Ready-to-eat cereals	0.04	0.08
Fats and Oils	Mayonnaise	0.02	0.02
Frozen Dairy Desserts and Mixes	Regular and low-fat ice creams and ice milks	0.01	0.01
	Frozen yogurt	0.01	0.01
Grain Products	Health bars	0.04	0.08
Milk, Whole, and Skim	Reduced-fat milks	0.01	0.01
Milk Products	Flavored milk based beverages	0.01	0.01
	Meal replacements	0.04	0.08
	Buttermilk	0.01	0.01
	Yogurt	0.02	0.02
Processed Fruits and Fruit Juices	Fruit juices	0.02	0.02
	Carbonated and fruit-flavored drinks	0.02	0.02

Appendix III

APPENDIX III

COMPARISON OF THE OLIGOMERIC AND MONOMERIC FLAVAN-3-OL DISTRIBUTION IN TWO COMMERCIAL GRAPE SEED EXTRACT PREPARATIONS

Table AIII-1 Comparison of the Oligomeric and Monomeric Flavan-3-ol Distribution in Two Commercial Grape Seed Extract Preparations		
Analyte	**Grape Seed Extract (GSE)**	**Gravinol Super™[1]**
Protein (%)	3.08 to 6.10	1.06%
Ash (%)	0.25 to 0.70	0.8%
Fat (%)	0.13 to 0.58	None reported
Carbohydrate (%)	6.33 to 9.37	None reported
Moisture (%)	2.52 to 4.99	2.24%
Total Oligomeric Flavan-3-ols (%), (dry weight basis)	73.32 to 77.63	89.3
Oligomeric Distribution (%), (dry weight basis)		
Decamer and above	1.04 to 4.07	NA
Nonamer	4.54 to 5.78	NA
Octamer	4.11 to 10.86	NA
Heptamer	6.76 to 17.93	NA
Hexamer	10.15 to 17.64	NA
Pentamer	6.32 to 12.18	74.8 (pentamer and above)
Tetramer	9.02 to 13.51	2.9
Trimer	3.42 to 13.19	5.0
Dimer	7.41 to 10.10	6.6
Total Monomeric Flavan-3-ols (%), (dry weight basis)	2.60 to 4.08	6.6
Monomeric Distribution (%), (dry weight basis)		
(+)-Catechin	0.77 to 1.49	2.5
(-)-Epicatechin	0.83 to 1.39	2.2
(-)-Epigallocatechin	0.35 to 0.44	1.4
(-)-Epicatechin gallate	0.61 to 0.88	--
(-)-Epigallocatechin gallate	0.03 to 0.10	0.5
Flavan-3-ol Distribution[2]		
Monomers	<5.5 (~3.33)	6.6
Oligomers	~73.3[3]	≥14.5 and up to 89.3
Polymers	~2.44	Not determined
Ratio (Monomers:Oligomers + Polymers)	1:13.8[4]	1:13.5

NA = Not available

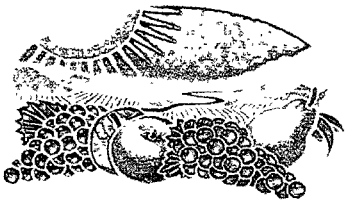
[1]Yamakoshi *et al.* (2002a)

[2]Distribution of GSE flavan-3-ols was determined by using the average of 5 batch analyses

[3]Calculated using an average level of oligomers of 75.74% – average level of decamers (polymers) of 2.44%

[4]Calculated using a level of 5.5% catechin monomers

End Submission



AM 

Providing World-Class, Natural Products To Improve People's Lives

March 5, 2003

03-03-11A10:30 RCVD

Dr. Robert Martin
Deputy Director
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food And Drug Administration
5100 Pain Branch Parkway
College Park, MD 20740-3835

Via Fax: 202-418-3428

Re: Authorization to Discuss Technical Issues with Dr. Joe Borzelleca
GRAS Notice No. GRN 000124

Dear Dr. Martin:

As the FDA moves forward with consideration of our GRAS application, technical questions may arise regarding the dossier. This correspondence hereby authorizes you to contact Dr. Joe Borzelleca directly to discuss safety/toxicological issues. As you know, Dr. Borzelleca served on the Scientific Panel. Dr. Borzelleca can be reached at 804-285-2004.

Please don't hesitate to call if you have any questions.

Sincerely,

Steven J. Anderson
Vice President

Cc: Joe Borzelleca (Fax: 804-285-1401)

009108

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